INITIAL CLINICAL REVIEW FOR INCLUSION IN ADVISORY COMMITTEE BRIEFING DOCUMENT

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Reviewer Name	Karen Murry Mahoney, MD
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Established Name	Exubera®
(Proposed) Trade Name	Exubera®
Therapeutic Class	Inhaled insulin
Applicant	Pfizer
Priority Designation	S
Formulation	Pulmonary inhalation powder for use with specified pulmonary inhaler
Dosing Regimen	Dose-titrated premeal inhalation
Indication	Treatment of hyperglycemia in Type 1 and Type 2 diabetes mellitus
Intended Population	Adult Type 1 and Type 2 diabetics

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1 EXECUTIVE SUMMARY

This Executive Summary contains a brief overview of the clinical review. The complete body of the review is somewhat lengthy, and contains numerous sections and tables. For the reader who wants a more complete summary than that found in the Executive Summary, Section 9.1, the Conclusions Section, contains an expanded discussion of most of the findings of the overall review. In Section 9.1, each point of discussion is followed by a section number for the pertinent section of the main body of the review. The reader can refer to the relevant section, if desired, for more complete information regarding the review of that topic.

This review is not final; additional information from the Advisory Committee and other review disciplines will be considered prior to finalization of the review and recommendations for regulatory action.

1.1 Recommendation on Regulatory Action

Not applicable at this time.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Not applicable at this time.

1.2.2 Required Phase 4 Commitments

Not applicable at this time.

1.2.3 Other Phase 4 Requests

Not applicable at this time.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Exubera®, developed by Pfizer, Inc., is a dry powder formulation of recombinant human insulin designed to be delivered systemically via pulmonary inhalation. Exubera® is to be delivered through a novel pulmonary inhaler developed by Nektar, Inc.; this inhaler was designed specifically for delivery of this insulin product.

Pfizer seeks indications for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia. Pfizer considers the drug comparable to rapid-acting insulin analogs in onset of action, and comparable to regular insulin in duration of action. For Type 1 diabetics, Pfizer proposes use of Exubera® in combination with a longer-acting insulin. For Type 2 diabetics, Pfizer proposes use as monotherapy, or in combination with oral agents or longer acting insulins.

Pfizer undertook an extensive clinical development program, with over 50 Phase 2 and Phase 3 clinical trials. Of these, the applicant considers five (106, 107, 108, 109 and 110) to be pivotal for both efficacy and safety, and two (1022 and 1029) to be pivotal for pulmonary safety. The applicant presented data from these trials for a total of 2,373 patients. Of these, 1,230 were exposed to inhaled insulin (alone or in combination with subcutaneous insulin or oral agents), 972 received only comparator subcutaneous insulin, and 171 received only comparator oral agents.

Across the entire development program, 4,959 patients were enrolled in trials. Of these, 3,603 received inhaled insulin, with 2,128 patients exposed to insulin during controlled Phase 2 and Phase 3 clinical trials. A total of 1,341 and 644 patients received subcutaneous insulin alone or oral agents alone, respectively, in Phase 2 and Phase 3 clinical trials. For Type 1 patients in controlled Phase 2 and Phase 3 trials, 698 patients had a total of 5,894 patient-months of inhaled insulin exposure. For Type 2 patients in controlled Phase 2 and Phase 3 trials, 1,277 patients had a total of 12,187 patient-months of inhaled insulin exposure. For all Phase 2 and Phase 3 studies, including extension studies, there were 16,571 patient-months of exposure for Type 1s and 30,688 patient-months of exposure for Type 2s. Total duration of exposure extended as far as seven years (13 patients), with 1,581 patients having >1 year of exposure, and 708 having >2 years of exposure.

1.3.2 Efficacy

The applicant seeks the following four indications:

- control of hyperglycemia in Type 1 diabetics (inhaled insulin in combination with a longer-acting insulin)
- control of hyperglycemia in Type 2 diabetes (inhaled insulin monotherapy)
- control of hyperglycemia in Type 2 diabetes (inhaled insulin in combination with oral agents)
- control of hyperglycemia in Type 2 diabetes (inhaled insulin in combination with longer-acting insulins)

Although the applicant does not seek an indication for the use of Exubera® in children, the clinical reviewer anticipates significant interest in the use of inhaled insulin in children, and therefore efficacy data regarding pediatric use were also considered.

In general, the major Phase 3 trials met the definition of "adequate and well-controlled" studies contained in 21 CFR 314.126. One concern regarding trial design was the method of treatment assignment. Patients were assigned to their treatment groups by block allocation within center rather than by true randomization, and it may have been possible for an investigator to predict the treatment group assignment of the next patient in a block. The investigator could then have

chosen a "better" patient if the investigator could predict that the next patient would go to the inhaled insulin group, or a "worse" patient to go to the SQ group. However, statistical analyses did not reveal evidence of bias related to this treatment allocation method. All studies were open label, and none used inhaler or injection placebos. Historically, clinical trials of insulin have generally not been blinded trials, due to safety, logistical, and ethical concerns.

For the most part, exclusion criteria used in Phase 2 and Phase 3 trials were unlikely to limit the general applicability of trial results. However, the following exclusion criteria could have excluded significant numbers of diabetics who might be encountered in clinical practice:

- BMI >35 kg/m^2 for Type 2 diabetics
- HbA1c >12%
- Renal impairment
- Requirement of >150 units per day of subcutaneous insulin
- Signs of autonomic neuropathy, such as gastroparesis or orthostatic hypotension
- Tobacco smoking within 6 months of study or during study
- Two or more serious hypoglycemic episodes within the year prior to study
- Hospitalization or emergency room visit (for poor diabetes control) within the six months prior to study

These limitations were considered during review.

The Exubera® inhaled insulin drug-device combination (referred to hereafter as "inhaled insulin" or "Exubera®") appears to be effective in control of hyperglycemia for the following indications:

- control of hyperglycemia in Type 2 diabetes (inhaled insulin monotherapy)
- control of hyperglycemia in Type 2 diabetes (inhaled insulin in combination with oral agents)
- control of hyperglycemia in Type 2 diabetes (inhaled insulin in combination with a longer-acting subcutaneous insulin)

The clinical reviewer has concerns regarding the proof of efficacy of this inhaled insulin for:

- control of hyperglycemia in Type 1 diabetics (inhaled insulin in combination with a longer-acting subcutaneous insulin)
- off-label use in Type 1 diabetic children and adolescents

There is a clear standard of care for the control of Type 1 diabetes; this standard was established by the findings of the Diabetes Control and Complications Trial (DCCT) of intensive insulin therapy. The applicant submitted Study 107 as an "intensive control" trial in which inhaled insulin as a premeal insulin was compared to regular subcutaneous insulin as a premeal insulin; both regimens included long-acting "basal" subcutaneous insulin. Although inhaled insulin was noninferior to subcutaneous insulin for change in HbA1c in this trial, neither treatment group achieved a mean HbA1c in the range achieved in the DCCT. Only 23% of inhaled insulin group patients achieved a HbA1c <7%. By the statistical model used by the applicant, rates of severe hypoglycemia appeared higher in the inhaled insulin group than in the subcutaneous insulin group. If an antidiabetic agent is noninferior, but not superior, in efficacy to an active control, rates of severe hypoglycemia should be comparable between groups, but this did not appear to be

the case using the applicant's statistical model. However, FDA Biostatistics review indicates that the model selected by Pfizer might not have been the best model to compare rates of severe hypoglycemia. FDA Biostatistics review is ongoing, but it appears that rates of severe hypoglycemia may actually not differ between treatment groups for Study 107.

Studies performed in children to date have not demonstrated that the desirable level of glucose control (i.e. that associated with decreased risk for later diabetic complications) can be reliably achieved with inhaled insulin.

1.3.3 Safety

A separate safety review is being conducted by the Division of Pulmonary and Allergy Drug Products. This review concerns nonpulmonary safety issues.

For deaths occurring in the development program, no clear differences were demonstrated between inhaled insulin patients and comparator patients for incidence or cause of death.

Nonpulmonary serious adverse events occurred with approximately equal frequency among inhaled insulin patients and comparator patients. Serious hypoglycemia was the most commonly reported serious adverse event, and occurred with similar frequency between inhaled insulin groups and subcutaneous groups for most studies, except, as mentioned above, for the intensive control trial in Type 1 diabetes. Adult patients in oral agent comparator groups were less likely to experience serious hypoglycemic adverse events than were patients in either inhaled insulin groups or subcutaneous insulin groups. Pediatric patients in inhaled insulin groups were more likely to experience severe hypoglycemia than pediatric patients in subcutaneous insulin groups. Diabetic ketoacidosis occurred with similar frequency among pediatric patients treated with inhaled insulin or subcutaneous insulin. In the controlled Phase 2 and Phase 3 trials, no other serious nonpulmonary adverse event appeared to occur with significantly greater frequency in inhaled insulin group patients than in comparator group patients for either adult or pediatric patients.

Hypoglycemia was evaluated in three ways; as a reported adverse event, as a protocol-defined secondary endpoint measure within individual studies, and as an overall safety measure using a separate definition. Hypoglycemia in general did not occur more frequently in inhaled insulin patients than in subcutaneous comparator patients. As discussed above, severe protocol-defined hypoglycemia occurred more frequently (by the applicant's analysis) in inhaled insulin group patients than in subcutaneous group patients in the intensive control trial in Type 1 diabetics, and in pediatric Type 1 diabetics. Among Type 1 diabetics, inhaled insulin group patients were more likely to experience prebreakfast hypoglycemia, while subcutaneous insulin group patients were more likely to experience prelunch hypoglycemia. The reason for this difference in time-of-day for occurrence of hypoglycemia is unknown; mean daily and evening doses of longacting insulin do not appear to have been higher in inhaled insulin group patients.

Among nonserious common adverse events, hypoglycemia was the most common adverse event for both Type 1 and Type 2 patients, but did not occur with greater frequency among inhaled

insulin group patients than among comparator group patients. Common adverse events which had a higher incidence among adult inhaled insulin group patients, and seem likely to be related to inhaled insulin use, include cough, and nasopharyngeal events such as pharyngitis, rhinitis and sinusitis. Adverse events related to the ear, including otitis media, appear likely to be related to inhaled insulin use in pediatric patients.

Rare but potentially serious adverse events which appeared to occur somewhat more frequently in inhaled insulin group patients than in comparator patients per unit of patient-time over all Phase 2/3 trials (controlled and uncontrolled) included the eye event terms "eye hemorrhage" and "retinal hemorrhage", and the event term "allergic reaction".

The development of insulin antibodies was common among inhaled insulin group patients. End-of-study titres, change from baseline in titres, and rates of seroconversion (from nonmeasurable to measurable) were all higher for inhaled insulin group patients than for comparators, for both Type 1 and Type 2 patients. Type 1 patients exhibited greater increases than Type 2 patients; children exhibited greater increases than adults; and women exhibited greater increases than men. Despite these laboratory findings, a clinical correlate was not found. Associations were not demonstrated between insulin antibody levels and hypoglycemia, allergic adverse events, or other adverse events. There was no clinical evidence of a neutralizing effect of these antibodies on insulin action, and no associations were found between insulin antibody levels and indices of glycemic control. Discontinuation of inhaled insulin resulted in a decline in insulin antibody levels.

Declines in pulmonary function tests for forced expiratory volume in one second (FEV1) and diffusion capacity for carbon monoxide (DLco) were more common in inhaled insulin group patients than in comparator group patients, and will be discussed in the pulmonary review.

Discontinuations due to adverse events were more common among inhaled insulin group patients than among comparator group patients. The most common category of adverse events leading to discontinuation was respiratory, and cough was the most common individual adverse event leading to discontinuation. The clinical reviewer noted a concern for possible investigator reporting bias in the assignment of reasons for discontinuation. A large number of discontinuations were listed as being due to "withdrawn consent" or "patient no longer willing to participate". The clinical reviewer requested further information regarding stated reasons for discontinuation among these patients. Some of these reasons appear to have been misclassified, and some were actually due to additional adverse events, lack of efficacy or device concerns. Misclassification appeared to have been more frequent among discontinuing patients in inhaled insulin groups than in comparator groups. Revision of these reasons for discontinuation led to greater differences between groups for discontinuations due to adverse events (both Type 1 and Type 2 patients), and discontinuations due to insufficient clinical response (Type 1 patients).

There was no clear difference in routine laboratory results between inhaled insulin group patients and comparator patients.

1.3.4 Dosing Regimen and Administration

In the DOSAGE AND ADMINISTRATION section of the proposed product label, the applicant proposes a similar regimen to that used in clinical trials. Administration 10 minutes prior to meals is proposed. Calculation of initial dosage based on body weight is proposed, with a formula: body weight (kg) x 0.05 mg, rounded down to nearest whole mg, = premeal dose, assuming 3 meals/day. The applicant does not propose instructions for transitioning from subcutaneous premeal insulin to inhaled insulin, based on the patient's current premeal subcutaneous insulin dose. No formula is presented for dosing by carbohydrate exchanges, and there are no recommendations for calculation of bedtime snack doses. The label does not include recommendations for titration increments. Mention is made of the fact that three 1 mg unit dose blisters result in greater insulin exposure than one 3 mg dose blister. The dosage and administration section does not mention a need for close monitoring by the patient and physician during initiation of inhaled insulin.

Dose proportionality and dose equivalence were not demonstrated for Exubera®.

In Study A2171012, dose proportionality was not demonstrated over a range of doses. In this study, dose proportionality of several dosages was compared, including doses of 1 mg (1x1 mg), 2 mg (2x1 mg), 3 mg (1x3 mg), 4 mg (1x3 mg + 1x1 mg) and 6 mg (2x3 mg). None of the 90% confidence intervals for any AUC comparison fell within bioequivalence boundaries (80-125%). Approximately 1/3 of all samples for Cmax and AUC for the 3 mg dose group had values below the mean observed for the 2 mg dose group.

Based on this study, it appears that the possibility exists that, in a given patient, the titrated "increase" from 2x1 mg to 1x3 mg could actually result in lower blood insulin AUC, rather than the expected increase in blood insulin. This could create a significant problem in upward titration of dose, particularly in the lower dosage ranges such as might be used in Type 1 diabetes. This problem would be magnified if the drug is used off-label for the treatment of pediatric Type 1 diabetics, who generally have lower body weights and therefore smaller initial insulin doses.

Dose equivalence was also not demonstrated for three 1 mg blisters and one 3 mg blister. In Study 1006, the AUC_{0-360} for 3 inhalations of 1 mg was approximately 40% higher than that for 1 inhalation of 3 mg, and Cmax was approximately 30% higher. This difference appears to be related in part (but not entirely) to a problem with the inhaler; it is much more efficient in breaking up the powder in blisters of a lower fill mass. Although the overall emitted mass is fairly similar for 3x1 mg and 1x3 mg, the 1 mg strength emits a higher proportion of particles <3.3 μM, which the applicant asserts is the particle size most capable of reaching the deep lung, and the particle size associated with optimal systemic absorption. However, the relative difference in fine particle dose for the 1 mg blister vs the 3 mg blister does not entirely account for the dose nonequivalence. In addition to the potential problems noted above with titration, patients must be instructed not to substitute three 1 mg inhalations for one 3 mg inhalation if they run out of their 3 mg blisters. This could result in greater insulin exposure and risk for hypoglycemia.

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increased risk for hypoglycemia when doses significantly above the mean are delivered. However, significant variability in absorbed dose is also a problem with subcutaneous insulin. Chemistry review is ongoing, and will address the acceptability of this variability in emitted dose.

While variability in delivery of insulin with Exubera® is a concern, it is noteworthy that marked variability in absorbed dose of insulin, and pharmacodynamic response, is also a major concern with subcutaneous insulin, and is well-described in the medical literature. Within this development program, significant variability in pharmacodynamic (glucose) response was seen for both inhaled and subcutaneous insulin, and the variability was comparable in standardized meal studies.

1.3.5 Drug-Drug Interactions

Study 1005 included pharmacokinetic data regarding co-administration of inhaled insulin and inhaled albuterol. While overall, inhaled insulin PK did not differ from 30 minutes pre- to 30 minutes post- albuterol, the small subset of emphysema patients (5/12 total COPD patients) had mean insulin exposure that was 46% higher post-albuterol than pre-albuterol.

Smokers have a 2-5 fold higher Cmax, Tmax and AUC for inhaled insulin than do nonsmokers. Smoking cessation leads to a decline in insulin exposure within 3 days of abstinence; by 7 days, insulin exposure is near that seen in nonsmokers. Resumption of smoking after abstinence results, within 2-3 days, in increases in exposure to levels similar to that seen prior to smoking cessation. The applicant's proposed product label states that smokers should not use inhaled insulin. Specific education of providers and patients may be necessary in order to reduce the likelihood that smokers will receive inhaled insulin.

No other drug-drug interaction studies were submitted with the NDA.

1.3.6 Special Populations

A clinical pharmacokinetic and pharmacodynamic study was conducted in gestational and pregestational diabetic pregnant women. This study showed similar relative pharmacokinetics between inhaled insulin and regular subcutaneous insulin to that seen in a separate study in nonpregnant Type 2 diabetics. Maximum decline in glucose concentration was less in pregnant diabetics exposed to inhaled insulin than that seen in nonpregnant Type 2 diabetics in a separate study, but baseline differences limit interpretability. In the overall development program, women who became pregnant during study were all discontinued from study per protocol. Rates of spontaneous pregnancy loss were not significantly higher in these patients than in pregnant diabetics described in the medical literature. There was one neonatal death (from congestive

heart failure) which occurred six months after the mother discontinued inhaled insulin; estimated exposure in utero had been 3-4 weeks.

In elderly obese Type 2 patients, inhaled insulin had an earlier insulin Tmax and a higher Cmax than regular subcutaneous insulin, but a similar AUC. This pattern is similar to that seen in nonelderly patients, but different dosing regimens did not permit direct comparisons.

Following administration of inhaled insulin, patients with chronic obstructive pulmonary disease (COPD) had a higher Cmax (by up to 50%) than healthy subjects without COPD. Tmax was earlier, and AUC was greater, in COPD patients than in healthy subjects.

The applicant did not submit studies of inhaled insulin use in renal or hepatic impairment.

2 INTRODUCTION AND BACKGROUND

This review was prepared utilizing the current "Center for Drug Evaluation and Research Clinical Review Template" (Jul 04 version), and the "Reviewer Guidance for Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review" (Feb 05 version). This template and guidance seek to provide consistency and ensure completeness in clinical reviews, and to allow subsequent readers to readily locate specific types of information. In certain areas of the review, this uniformity of format may sometimes result in writing that does not flow smoothly, and the reader may need to refer to the Table of Contents for location of a specific type of information. Also, the completeness required for each section under the template may result in some redundancy of information.

Conclusions reached in this review are the result of the clinical reviewer's evaluation of the clinical portions of the New Drug Application; nonclinical and clinical pharmacology portions are also undergoing evaluation by reviewers with expertise in the relevant areas, and these reviews may also affect decisions made by signatory authorities regarding approvability of this application.

2.1 Product Information

Pfizer, Inc. has developed a dry powder formulation of recombinant human insulin designed to be delivered systemically via pulmonary inhalation. This product, under the proposed trade name Exubera®, is to be delivered through a novel pulmonary inhaler developed by Nektar, Inc.; this inhaler was designed specifically for delivery of this insulin product. Because of the novel characteristics of this insulin formulation, and because this is the first inhaled insulin:pulmonary inhaler drug-device combination to be considered for marketing, this is considered to be a new molecular entity.

Pfizer seeks indications for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia. Pfizer considers the drug comparable to rapid-acting insulin analogs in onset of action and duration of action. For Type 1 diabetics, Exubera® is to be used in combination with a longer-acting insulin. For Type 2 diabetics, Pfizer proposes use as monotherapy, or in combination with oral agents or longer acting insulins.

2.2 Currently Available Treatment for Indications

Type 1 diabetes is currently treated almost exclusively with subcutaneously administered insulin, which is available in a variety of formulations and analogs, with a spectrum of time-action profiles. Because Type 1 diabetics have virtually no residual pancreatic islet beta cell function, these patients have an absolute requirement for administered insulin for survival, and cannot be managed with diet and exercise alone. Patients generally receive one or two subcutaneous injections per day of a relatively long-acting insulin as "basal" insulin, and take a short-acting subcutaneous insulin before each meal. Continuous subcutaneous infusion via insulin pump of short-acting insulin, with mealtime boluses, is also used. Pramlintide, an amylin analog, was

recently approved as the first agent other than insulin for treatment of Type 1 diabetes, but pramlintide is adjunctive to mealtime insulin, rather than substitutable for subcutaneous insulin.

Type 2 diabetics often undergo an initial trial of diet and exercise. If control is inadequate, a variety of oral agents are available. Classes include sulfonylureas; other oral insulin secretagogues (such as repaglinide and nateglinide); the biguanide metformin; thiazolidinediones; α-glucosidase inhibitors; and the amylin analog pramlintide. If adequate blood glucose control is not achieved with oral agents, subcutaneous insulin is often used.

The applicant considers Exubera® comparable in time-action profile to rapid-acting insulin analogs, which have a rapid onset of action (about 15 minutes), a short time to peak action (0.5-1.5 hours), and a short duration of action (2-5 hours). Currently marketed rapid-acting analogs available in the United States include insulin aspart and insulin lispro. Regular soluble crystalline zinc insulin is also used as a premeal insulin; it has an onset of action at 30-45 minutes, peak action between 1.5 and 4 hours, and a duration of action of 5-8 hours.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient used in the production of the inhalation powder is a recombinant human insulin which is not approved for marketing in the United States. the manufacturer of the active ingredient insulin, has authorized Pfize is under review by the FDA Office of Drug Chemistry.

2.4 Important Issues With Pharmacologically Related Products

No other inhaled insulins are approved in any country. In published research reports in the medical literature, concerns are mostly related to the question of longterm pulmonary safety (Royle 2004).

2.5 Presubmission Regulatory Activity

During the development of Exubera®, there were many meetings and written communications between FDA and the sponsors. The following are highlights of some of those interactions:

31 Aug 93: Investigational New Drug Application (IND) 43313 was submitted to the Division of Metabolic and Endocrine Drug Products (DMEDP) by Inhale Therapeutics, which is now Nektar Therapeutics, the manufacturer of the pulmonary inhaler used in this application.

17 May 95: IND ownership was transferred to Pfizer, Inc.

6 May 96: Meeting with FDA to discuss development plans. FDA placed emphasis on longterm pulmonary safety data and characterization of pharmacokinetics. Concerns were raised regarding the lack of a blinded comparator.

2 Jun 98: Supplier of recombinant human insulin was changed from

3 Jun 98: End-of-Phase-2 Meeting. General agreements reached regarding the proposed Phase 3 clinical program. Concerns regarding longterm pulmonary safety again stressed by FDA.

15 Mar 99: Teleconference regarding pulmonary safety evaluation plans. FDA stated that longterm comparative pulmonary safety trials were needed.

10 Aug 99: Letter to sponsor from FDA stating that Written Request for Pediatric Studies would not be issued at that time.

18 Aug 00: Pulmonary safety meeting. FDA stated that the size of the proposed pulmonary safety database might be inadequate for NDA approval, and requested study of patients with underlying lung disease.

16 Apr 01: Pulmonary safety meeting. FDA pulmonary reviewer stated that 1-year controlled safety data on 200 Type 2 patients from other efficacy studies might not be adequate, due to small patient numbers and short duration of exposure. FDA stated that the proposed overall pulmonary safety database might be inadequate due to lack of adequate longterm controlled pulmonary safety data and lack of adequate efficacy/safety information in patients with concurrent lung diseases such as asthma and chronic obstructive pulmonary disease (COPD). Data for pulmonary safety in Type 1 patients also requested. FDA stated that subset analyses from other studies might not be adequate for evaluation of longterm safety in patients with underlying lung disease. FDA requested controlled study, for ≥ 1 year, of patients with COPD (n ≥ 100), asthma (n ≥ 100), and Type 1 diabetics with underlying lung disease (n ≥ 100).

5 Apr 02: Meeting regarding monotherapy studies and pulmonary safety issues. FDA again requested controlled study, for ≥ 1 year, of patients with COPD (n ≥ 100), asthma (n ≥ 100), and Type 1 diabetics with underlying lung disease (n ≥ 100), and stated that this information must be included with the initial NDA application.

29 Jul 02: Letter to sponsor requesting controlled high resolution computerized tomography (HRCT) data and lung biopsies in a subset of patients.

15 Nov 02: Teleconference regarding FDA requests for lung high resolution computerized tomography (HRCT) and lung biopsies for antigen-antibody complexes. FDA expressed concern regarding a decline seen in pulmonary function tests at six months, for forced expiratory volume in 1 second (FEV1) and lung diffusing capacity for carbon monoxide (DLCO). FDA requested HRCT for 50 patients on Exubera® and 50 patients on control at zero and 24 months. FDA

requested that ongoing and future protocols include specific indications for pulmonary consultation for patients with the highest titres of circulating anti-insulin immunoglobulin G (IgG). FDA again expressed concern about possible immune complex deposition or other immune processes at the level of the alveolae and interstitium, and requested lung biopsies, with immunostaining, in 5-10 patients.

12 Dec 02: Letter to sponsor stating that, for efficacy and safety studies in Type 1 patients, both the inhaled insulin and subcutaneous (SQ) insulin groups must achieve HbA1cs that demonstrate tight glycemic control. The agency reiterated its previous requests for adequate pulmonary safety data at the time of NDA submission.

8 Dec 03: Letter to sponsor expressing concern about sponsor's proposal to study fewer patients with underlying lung disease. Reiterated previous requests for controlled study, for ≥ 1 year, of patients with COPD (n ≥ 100), asthma (n ≥ 100), and Type 1 diabetics with underlying lung disease (n ≥ 100).

28 Jun 04: Pre-NDA meeting. FDA stated that the proposed efficacy and general safety databases appeared to be adequate to allow for review. The Division of Pulmonary and Allergy Drug Products (DPADP) stated that, for years, DPADP had been giving a clear and consistent message regarding the importance of pulmonary safety in the ultimate review of an Exubera® NDA. DPADP also stated that the duration of exposure and the proposed number of patients for whom data would be submitted in the underlying pulmonary disease protocols were far below that requested by DPADP on multiple occasions in prior meetings. Pfizer proposed submission of additional pulmonary safety data during the review cycle, but DPADP emphasized that the NDA should be complete upon submission.

2.6 Other Relevant Background Information

Exubera® is not approved for marketing in any country.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

3.2 Animal Pharmacology/Toxicology

As of 27 Jun 05, the Animal Pharmacology and Toxicology review is still ongoing. Major preclinical issues have not been identified to date. However, animal studies were performed in nondiabetic animals, resulting in significant limitations of testing due to animal hypoglycemia. Longterm safety data in animals are not available. Animal carcinogenicity and reproductive toxicity studies were not performed. If the toxicologic reviewer notes concerning findings upon final review, discussion will follow regarding potential clinical relevance.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary sources of clinical data for this review were the clinical trial data submitted by the applicant. The clinical reviewer also conducted an independent literature review. The Division of Pulmonary and Allergy Drug Products is conducting a separate review of the pulmonary safety of the product; this review is ongoing as of 27 Jun 05. The Endocrine and Metabolic Drugs Advisory Committee is scheduled to meet on 8 Sep 05 regarding this product.

4.2 Tables of Clinical Studies

The following tables list all clinical studies submitted with the original NDA. They are grouped by diabetes type (1 or 2), and by study type (efficacy and safety, or clinical pharmacology).

Table 4.2.1 Controlled Clinical Efficacy and Safety Studies in Type 1 Diabetics

Study Number	Study Type	Inhaled Insulin Regimen	Control Grp	n	Duration	Considered "Pivotal" by Applicant?
217-102	R[1], OL[2], PG[3]; inh ins vs "conventional" SQ[9]	TID[4] ac[5] inh ins + hs[6] UL[7]	subject's usual SQ (BID or TID)	35 inh ins, 37 SQ	3 mo	n
217-106	R, OL, PG; inh ins vs "conventional" SQ	TID[4] ac inh ins + hs UL	SQ regular insulin ac brkfst and supper + NPH[8] ac brkfst and hs	170 inh ins, 164 SQ	6 mo	y
217-107	R, OL, PG; inh ins vs "intensive" SQ	TID ac inh ins + NPH ac brkfst and hs	SQ regular insulin TID ac + NPH ac brkfst and hs	162 inh ins, 165 SQ	6 mo	y
A2171009	R, OL, PG; children ages 6-11, inh ins vs "conventional" SQ	TID ac inh ins + hs UL or hs NPH or BID UL or BID NPH	SQ regular or lispro insulin ac brkfst and supper + q day or BID UL or NPH (2nd UL or NPH ac supper or hs)	61 inh ins, 59 SQ	3 mo	n

1 randomized
2 open-label
3 parallel group
4 three times daily
5 before meals
6 at bedtime
7 Ultralente® insulin
8 neutral protamine Hagedorn insulin
9 subcutaneous

Table 4.2.2 Ongoing Clinical Efficacy and Safety Studies in Type 1 Diabetics

Study Number	Study Type	Inh Ins Regimen	Control Grp	n	Duration	Considered "Pivotal" by Applicant?
A2171022	R, OL, PG; general safety and pulmonary safety	titrated premeal inh ins + hs UL, NPH or insulin glargine	SQ premeal lispro, regular or aspart + hs UL, NPH or insulin glargine	randomized 291 inh, 291 SQ; completed 12 months 238 inh, 258 SQ	2 yrs planned	y

Table 4.2.3 Controlled Clinical Efficacy and Safety Studies in Type 2 Diabetics

Study Number	Study Type	Inhaled Insulin Regimen	Control Group	n	Duration	Considered "Pivotal" by Applicant?
217-103	R, OL, PG; inh ins vs "conventional" SQ in Type 2s already on insulin	TID ac inh ins + hs UL	subject's usual SQ (BID or TID)	28 inh, 28 SQ	3 mo	n
217-104	R, OL, PG; inh ins + OAs[1] vs OAs in pts not well-controlled on OAs	TID ac inh ins + subject's usual OAs	subject's usual OAs	33 inh + OA, 36 OA	3 mo	n
217-108	R, OL, PG; inh ins vs "conventional" SQ in pts already on stable SQ regimen	TID[4] ac inh ins + hs UL	SQ regular and NPH, both BID ac brkfst and supper	149 inh, 149 SQ	6 mo	y
217-109	R, OL, PG; inh ins	TID ac	continued combo	105 inh alone,	3 mo	y

Table 4.2.3 Controlled Clinical Efficacy and Safety Studies in Type 2 Diabetics

Study Number	Study Type	Inhaled Insulin Regimen	Control Group	n	Duration	Considered "Pivotal" by Applicant?
	monotherapy vs combo OAs in pts not well-controlled on combo OAs	monotherapy or TID ac + continued combo OA	OA	102 inh + OA, 102 OA		
217-110	R, OL, PG; inh ins vs rosiglitazone	TID ac	rosi[2] 4 mg BID ac brkfst and supper	76 inh, 69 rosi	3 mo	y
A2171001	R, OL, PG; inh ins + SU[3] vs met + SU in pts poorly controlled on SU	TID ac + SU	met[4] + SU	222 inh + SU, 201 met + SU	6 mo reported of planned 2 yr study	n
A2171002	R, OL, PG; inh ins + met vs SU + met in pts poorly controlled on met	TID ac + met 1 gm BID	glibenclamide (max 5 mg BID) + met 1 gm BID	239 inh + met, 231 glibenclamide + met	6 mo reported of planned 2 yr study	n
A2171001/ A2171002 combined 2 yr final report	R, OL, PG	TID ac + met 1 gm BID or SU	baseline met 1 gm BID or baseline SU + either met or glibenclamide	471 inh, 441 combo OAs	2 yrs	n
A2171027	R, OL, PG; short-term pulmonary safety and PFT study	TID ac x 12 weeks, then SQ x 12 weeks	SQ x 24 wks	110 inh ins then SQ, 116 SQ only	3 mo with comparator, 3 mo followup SQ	n

1 oral diabetic agents
2 rosiglitazone
3 sulfonylurea
4 metformin

Table 4.2.4 Ongoing Clinical Efficacy and Safety Studies in Type 2 Diabetics

Study Number	Study Type	Inh Ins Regimen	Control Group	n	Duration	Considered "Pivotal" by Applicant?
A2171017	R, OL, PG; inh ins vs rosi as add-on for pts poorly controlled on SU + met	inh ins + met +/- SU	met + rosi	74 randomized	52 wks planned	n
A2171029	R, OL, PG; inh ins vs SQ pulmonary safety study	titrated premeal inh ins + hs UL, NPH or insulin glargine	SQ premeal lispro, regular or aspart + hs UL, NPH or insulin glargine	randomized 316 inh, 314 SQ; completed 12 months = 228 inh, 235 SQ	2 yrs planned	y

Table 4.2.5 Ongoing Pulmonary Safety Studies

Study Number	Study Type	Inh Ins Regimen	Comparator	n	Duration	Considered "Pivotal" by Applicant?
A2171028	R, OL, PG, in pts with asthma	TID ac + hs or BID long-acting insulin[1] SQ	TID short-acting SQ + hs or BID long-acting SQ	randomized 45 inh, 49 SQ; completed 7 inh, 10 SQ	15 mo planned	n
A2171030	R, OL, PG, in pts with COPD	TID ac + hs or BID long-acting SQ	TID short-acting SQ + hs or BID long-acting SQ	randomized 30 inh, 27 SQ; completed 8 inh, 6 SQ	15 mo planned	n

1 hs UL or glargine; or BID UL or NPH

Table 4.2.6 Uncontrolled Clinical Studies in Combined Type 1 and Type 2 Diabetics

Study Number	Study Type	Inh Ins Regimen	Comparator Regimen	n	Duration	Considered "Pivotal" by Applicant?
217-111	OL extension of multiple Phase 3 trials; later randomized withdrawal to examine PFT effects after withdrawal	TID inh ins ac + long-acting insulin or OA (continued throughout extension)	TID inh ins ac + long-acting insulin or OA for up to 36 months; then randomized withdrawal	Prior to randomized withdrawal, 664 Type 1s and 626 Type 2s; after randomized withdrawal, 394 cont inh ins and 415 discontinued inh ins	up to 36 months before randomized withdrawal; 6 months after randomized withdrawal	n
A2171036	OL extension of other extension protocols (102E, 103E and 104E)	inh as short-acting diabetic treatment +/- other long-acting diabetic treatments	no control	62 ongoing	up to 4 years	n

Table 4.2.7 Clinical Pharmacology Studies in Healthy Subjects

Study Number	Study Type	Inh Ins Regimen	Comparator Regimen	n	Duration
217-003	R, OL, 3-way X-over[1]; examine effect of increased # of inhalations on plasma insulin concentrations	1x1 mg 2x1 mg 3x1 mg	n/a	18	1 day/tx
A2171012	R, OL, 6-period X-over; dose proportionality and PK[2] using 1 and 3 mg dose combinations	1, 2, 3, 4 and 6 mg	n/a	25	single dose x 2 days
HA001	OL, self-controlled; compare bioavailability of inh vs SQ	0.32 U/kg, 0.5 U/kg	SQ regular insulin, 0.2 U/kg	24	1 dose q 2 weeks (total 5 wks)
217-001	R, OL, 3-way X-over; compare dose proportionality of 1 and 3 mg inh ins	3x1 mg 1x3 mg	SQ regular insulin 0.15 U/kg	24	1 day/tx
217-011	R, OL, 3-period, 3-tx X-over; examine effect of change in rate of inhalation	3 mg; inhalation rates of 10, 25, and >35 L/min	n/a	12	1 day/tx
217-002	R, OL, 3-way X-over; examine effect of 3 different breathing regimens	3 mg; "standard" breathing maneuver, breathing preceded by forced exhalation, forced exhalation + 3 maximum inspirations	n/a	14	1 day/tx
217-004	R, OL, 2-tx, 3-period X-over; intrasubject variability in insulin and glucose response, and effect of breath-hold	3 mg on days 1 and 8; 3 mg on day 15 without breath-holding	n/a	20	1 day/tx
217-012	R, OL, 4-period, 4-way X-over; compare closed and open chamber top position with different insulins	P2 inhaler with 3 mg Lilly insulin, P3 inhaler with HMR[1] insulin and closed chamber top, P3 inhaler with HMR insulin and open chamber top	10 u SQ regular insulin	23	1 day/tx
217-014	R, OL, 3-period, 3-way X-over; compare particle size and breath-holding effects	2 mg as 3.4 μM; 2 mg as 2.2 um with breath-holding; 2 mg as 2.2 μM without breath-holding	n/a	24	1 day/tx
217-019	R, OL, 3-period, 3-way X-over; effect of controlled inhalation rate and reduced particle size	2 mg, 3.4 um, inhal rate 25 L/min; 2 mg, 3.4 um, 10 L/min; 2 mg, 2.2 um, 10 L/min	n/a	25	1 day/tx
217-015	R, OL, 2-period, 2-way X-over; effect of fill weight	2 mg; fill weights = 1.7 mg powder/blister (60% insulin) or	n/a	27	1 day/tx

Table 4.2.7 Clinical Pharmacology Studies in Healthy Subjects

Study Number	Study Type	Inh Ins Regimen	Comparator Regimen	n	Duration
		5 mg powder/blister (20% insulin)			
A2171006	R, OL, 5-period, X-over; bioavailability of 1 and 3 mg blisters compared to SQ; within subject variability of 1 and 3 mg blisters	3x1 mg 1x3 mg	9 U SQ regular insulin	27	1 dose/ tx period
A2171015	R, OL, 5-period X-over; bioequivalence of Phase 3 and commercial formulations of 1 mg	1 mg Phase 3 formulation; 1 mg commercial formulation	3 U SQ regular insulin	79	inh 1 dose x 2 days; SQ 1 dose x 1 day
A2171014	R, OL, 5-period X-over; bioequivalence of Phase 3 and commercial formulations of 3 mg	3 mg Phase 3 formulation, 3 mg commercial formulation	9 U SQ regular insulin	51	inh 1 dose x 2 days; SQ 1 dose x 1 day
217-008	R, OL, 3-period, 3 tx X-over; effect of change in particle size on site of deposition in lung, and on PK/PD	2 mg of 4 μM; 2 mg of 2 μM; 1 mg of 1 μM	n/a	13	1 day/tx
217-007	R, OL, 2-period, X-over; bioavailability in obese subjects	3 mg	10 u SQ regular insulin	12 obese, 12 nl wt	1 day/tx
217-006	R, OL, 2-period X-over; bioavailability in adolescents ages 12-17 yrs	2x1 mg in subjects < 50 kg body wt; 1x3 mg in subjects >50 kg body wt	0.15 u/kg regular insulin SQ	20 inh; 20 SQ	1 day/tx
217-010	R, OL, 3-period; effect of rhinoviral challenge vs saline on insulin concentrations	3 mg on days 1, 3 and 4	n/a	20 rhinovirus, 4 saline	3 days
A2171016	R, OL, 4-way X-over; PK/PD in healthy Japanese men	1, 3 and 6 mg	12 U regular insulin SQ	16	1 dose/ tx period
217-023	R, OL, 3-period, 3 tx, X-over; Japanese and Caucasian males	1 and 2 mg, Japanese vs Caucasian	6 U regular insulin SQ, Japanese vs Caucasian	12 Japanese, 13 Caucasian	1 dose/tx period
217-005	R, OL, 2-period, 2 tx, X-over; bioavailability in smokers	1 mg	0.15 U/kg regular insulin SQ	24	1 day/tx
217-016	R, OL, PG; effect of cessation of smoking on bioavailability	2 mg, smokers vs nonsmokers	6 U regular insulin SQ	38 smokers, 30 nonsmokers	1 day/tx
A2171020	R, OL; effect of short-term smoking cessation	1 mg; smokers willing to quit for 7 days vs nonsmokers	3 U SQ regular insulin	20 smokers, 10 nonsmokers	2 single doses for nonsmokers; 6 single doses for smokers
217-017	R, OL, 3-period, 3-way X-over; euglycemic clamp to compare PK/PD of inh ins, lispro and regular insulin	2x3 mg	18 U lispro SQ or 18 U regular insulin SQ	18 inh, 17 lispro, 17 regular insulin	1 day/ tx period

1 Hoechst-Marion-Roussel

Table 4.2.8 Clinical Pharmacology Studies in Type 1 Diabetics

Study Number	Study Type	Inh Ins Regimen	Comparator Regimen	n	Duration
217-021	R, OL, 4-period X-over; compare PK/PD inh ins to SQ	3, 4, or 6 mg	9, 12, or 18 U patient's usual short-acting premeal insulin	22	1 dose/ tx period
217-018	R, OL, 2-period X-over; ages 6-17	1 mg (wt 20-34.9 kg); 2 mg (wt 35-49.9 kg); 3 mg (50-64.9 kg)	SQ 3 U (20-34.9 kg); 6 U (35-49.9 kg); 9 U (50-64.9 kg)	13 pediatric (ages 6-11); 14 adolescent (ages 12-17)	1 day
A2171026	R, OL, PG; examine week 24 change from baseline in postprandial glucose	TID ac titrated + BID NPH	TID ac titrated SQ regular insulin + BID NPH	24 inh, 23 SQ	24 weeks

Table 4.2.9 Clinical Pharmacology Studies in Type 2 Diabetics

Study Number	Study Type	Inh Ins Regimen	Comparator Regimen	n	Duration
217-101	R, OL, 4-period X-over; compare PK/PD inh ins to SQ	1 mg/18 kg	0.2 U/kg SQ insulin	16	1 dose/ tx period
A2171004	R, OL, 4-way X-over; compare inh vs SQ bioavailability in elderly obese patients	4 mg for pts < 150 kg wt; 6 mg for pts ≥ 150 kg wt	12 U SQ for pts <150 kg wt; 18 U SQ for pts ≥ 150 kg wt	20	2 doses ea tx on separate days
A2171003	R, OL, 4-way X-over; euglycemic clamp, intra- and inter- subject variability in smokers and nonsmokers	6 mg	18 U SQ	15 smokers, 14 nonsmokers	1 day/tx

Table 4.2.10 Clinical Pharmacology Study in Pregnant Diabetics

Study Number	Study Type	Inh Ins Regimen	Comparator Regimen	n	Duration
A2171007	R, OL, 2-period X-over; pregnant gestational diabetics and pregnant pregestational Type 2 diabetics	3 mg	9 U SQ	10 gestational, 3 pregestational	1 dose/ tx period

Table 4.2.11 Clinical Pharmacology Studies in Patients with Underlying Lung Disease

Study Number	Study Type	Inh Ins Regimen	Comparator Regimen	n	Duration
217-009	OL, 3-period X-over; bioavailability in mild asthmatics vs healthy nondiabetics	1x1 mg 1x3 mg	0.15 U/kg regular SQ insulin	24 asthma; 12 nl	1 day/tx
A2171005	R, OL, X-over; bioavailability in mild COPD pts vs healthy nondiabetics; examine effect of bronchodilator on bioavailability	1x3 mg; albuterol before and after	9 U SQ regular insulin; albuterol before and after	26 COPD; 12 nl	1 dose/ tx period

4.3 Review Strategy

For the efficacy review, the clinical reviewer emphasized evaluation of the controlled Phase 3 trials. For the safety review, the clinical reviewer emphasized review of the controlled Phase 2 and Phase 3 studies for comparison of rates of events. Safety review was augmented by review of all serious adverse event data from all human trials.

Separate reviews are being conducted by Biostatistics (separate reviewers for safety and efficacy), Animal Pharmacology and Toxicology, Biopharmacology, Chemistry (multiple reviewers), and Microbiology.

4.4 Data Quality and Integrity

The Division of Metabolic and Endocrine Drug Products has requested that the Division of

. As of 27 Jun 05, the results of these audits are not in the Division File System archive.

4.5 Compliance with Good Clinical Practices

All subjects in all trials were required to provide informed consent. Review of the consent forms for the Phase 3 studies revealed adequate descriptions of the potential risks of participation. The applicant documented protocol violations when they occurred. Major protocol violations were sometimes cause for discontinuation from study, as further discussed in Section 7.1.3. The Division of Scientific Investigations is conducting audits for site-specific issues regarding good clinical practices; the results of these audits are not in the Division File System as of 27 Jun 05.

In general, the applicant and previous sponsors involved in the development of this product appear to have complied with the principles of good clinical practice.

4.6 Financial Disclosures

The applicant provided financial disclosure in keeping with 21 CFR 54.2. For the 2,336 investigators involved in studies of Exubera®, the applicant obtained financial disclosure forms from all but 80. The applicant demonstrated due diligence in attempting to obtain forms from these investigators, with at least two written requests and two phone calls for each investigator. A total of 137 investigators had financial information to disclose in the form of equity interest or significant payments of other sorts (SPOOS) exceeding $25,000. Financial disclosure forms for all these investigators are included in the NDA, Module 1, Section 1.3.6.5. Because of the large number of investigators with significant equity or payments of other sorts, the clinical reviewer limited review to those individual investigators with in financial disclosures. The following table summarizes those disclosures, and notes the study for which the investigator had the largest financial disclosure, the center number, and the number of patients contributed from that center.

Table 4.6.1 Financial Disclosure Information for Investigators Disclosing in Equity Interest or Significant Payments of Other Sorts (SPOOS)

Total Amount Disclosed	Investigator	SPOOS	Equity	Studies[1]	Centers	# Subjects from Center

Table 4.6.1 Financial Disclosure Information for Investigators Disclosing in Equity Interest or Significant Payments of Other Sorts (SPOOS)

Total Amount Disclosed	Investigator	SPOOS	Equity	Studies[1]	Centers	# Subjects from

In order to assess whether the financial interests held by these investigators could have influenced the outcome of any of the affected studies, the following table examines the data by study, center, and total financial interests of investigators disclosing per investigator.

Table 4.6.2: Financial Interests by Center of Investigators Disclosing

Study	Total Patients in Study	Total Patients in Study Contributed by Centers with Inve Disclosing (% of Total Patients in Study)	Center	Total Patients in Center	Total Financial Interest per Center for Investigators Disclosing	Total Financial Interest per Study for Investigators Disclosing

The statistical review team (Drs. Mele and Buenconsejo) reanalyzed the primary efficacy endpoint for and the primary safety endpoints for , excluding the study centers in the above table. For results for the primary efficacy endpoint (change in remained highly statistically significantly in favor of the inhaled insulin group, even when those centers with large investigator financial disclosures were excluded (p value including all centers = <0.0001; p value excluding high financial interest centers = 0.0007). For , the difference between treatm t groups for change in months was nonsignificant when including all centers, and remained nonsignificant when excluding high financial interest centers.

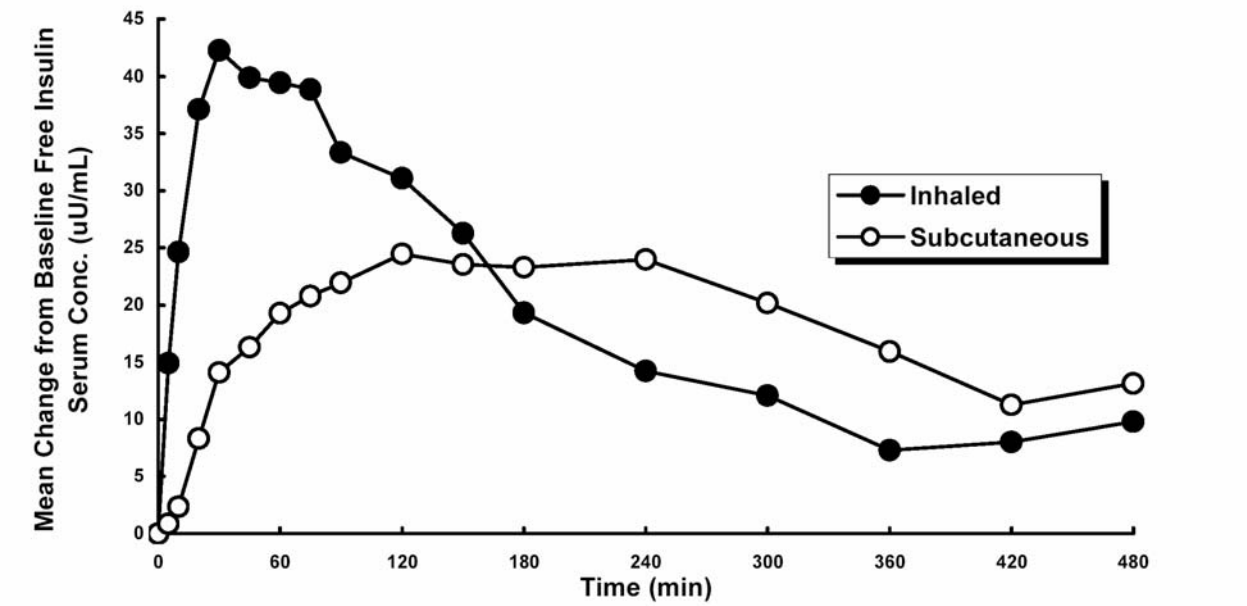
5 CLINICAL PHARMACOLOGY

As of 4 Aug 05, the Biopharmacology review of Exubera® is ongoing. The information below is extracted from the applicant's summary information. The clinical reviewer does not have expertise in this area, and the Biopharmacology review should be considered to represent the most accurate FDA interpretation of the NDA findings regarding clinical pharmacology.

5.1 Pharmacokinetics

In all Pharmacokinetic (PK studies), subcutaneous regular insulin was used as a comparator. Inhaled insulin is more rapidly absorbed than regular SQ insulin (Tmax 38-78 minutes vs Tmax 83-258 minutes). Postprandial Cmax is similar for inhaled insulin and regular SQ insulin, but fasting Cmax for inhaled insulin is higher. The following figure illustrates the concentration-time profile of inhaled insulin and regular SQ insulin.

Figure 5.1 Mean Change from Baseline in Serum Concentration of Free Insulin in Nonsmoking Patients with Type 2 Diabetes Mellitus Following Administration of 2x3 mg Inhaled Insulin or 18 U SQ Regular Insulin



Source: Module 2.7.2, Figure 2

Bioavailability was evaluated in adults with Type 1 diabetes (Study 021), adults with Type 2 diabetes (Study 1003), children and adolescents with Type 1 diabetes (Study 018), elderly obese patients with Type 2 diabetes (Study 1004), and pregnant gestational/pregestational diabetics (Study 1007). Among these various diabetic populations, mean bioavailability of inhaled insulin relative to SQ insulin was 10% (range 8-11%).

Dose proportionality and dose equivalence could be of clinical concern.

Dose proportionality was not demonstrated over a range of doses in Study A2171012. In this study, dose proportionality of several dose combinations was compared, including doses of 1 mg (1x1 mg), 2 mg (2x1 mg), 3 mg (1x3 mg), 4 mg (1x3 mg + 1x1 mg) and 6 mg (2x3 mg). None of the 90% confidence intervals for any AUC comparison fell within bioequivalence boundaries (80-125%).

When examining the actual individual subject data from the trial, one notes that multiple samples obtained for insulin Cmax and AUC for 3 mg dosing had lower values than the mean seen for 2 mg dosing. For Cmax, 10/29 samples obtained for Cmax at the 3 mg dose fell below the mean Cmax for the 2 mg dose. In this study, each patient generally only received 3 of the 5 dose combinations. A total of 6 patients received both the 2 mg dose and the 3 mg dose (doses given at different times during study). Among these 6 patients (each of whom had 2 Cmax values recorded for each dose), 4/6 had a Cmax value for the 3 mg dose that was lower than a Cmax

value for the 2 mg dose. A total of 6/26 samples for the 6 mg dose had lower Cmax values than the mean for the 4 mg dose, and 2/6 patients who received both the 4 mg dose and the 6 mg dose had a Cmax value for the 6 mg dose that was lower than a Cmax value for the 4 mg dose.

Similar findings are noted for AUC at each time interval, as illustrated in the following table:

Table 5.1.1 Overlap of Insulin AUC Values Between 2 mg and 3 mg Inhaled Insulin Doses, Study A2171012

	AUC 0-60	AUC 0-120	AUC 0-360	AUC 0-600
Number and percentage of AUC samples for 3 mg dose with lower AUC then the mean AUC for the 2 mg dose	8/29 (28%)	9/29 (31%)	8/29 (28%)	10/29 (34%)
Number and percentage of AUC samples for 6 mg dose with lower AUC then the mean AUC for the 4 mg dose	6/26 (23%)	4/26 (15%)	6/26 (23%)	7/26 (27%)
Number and percentage of patients who had both a 3 mg and 2 mg dose, who had a lower AUC value at the 3 mg dose than a 2 mg dose AUC[1]	4/6 (67%)	2/6 (33%)	2/6 (33%)	3/5 (60%)
Number and percentage of patients who had both a 6 mg and 4 mg dose, who had a lower AUC value at the 6 mg dose than a 4 mg dose AUC	4/6 (67%)	2/6 (33%)	2/6 (33%)	2/6 (33%)

1 Each patient had two measurements for each AUC time interval.

This could lead to clinical problems with dose titration; if a clinician advises a patient to increase their dose of inhaled insulin from 2 mg to 3 mg, expecting an increased exposure and/or concentration of insulin, the patient could actually have a paradoxic decrease in exposure and/or concentration. This could be a problem for patients in the lower dosage ranges, e.g. Type 1 diabetics and children. If these patients have high blood sugar levels at 2 mg, and are deemed to need more insulin action, they could actually achieve lower insulin levels with an "increase" to 1x3 mg, and develop paradoxically higher blood sugars. For the brittle Type 1 diabetic, these changes could be significant.

Dose equivalence was also not demonstrated for three 1 mg blisters and one 3 mg blister. In Study 1006, the AUC_{0-360} for 3 inhalations of 1 mg was approximately 40% higher than that for 1 inhalation of 3 mg, and Cmax was approximately 30% higher. This difference appears to be related in part (but not entirely) to a problem with the inhaler; it is much more efficient in breaking up the powder in blisters of a lower fill mass. Although the overall emitted mass is fairly similar for 3x1 mg and 1x3 mg, the 1 mg strength emits a higher proportion of particles <3.3 μM, which the applicant asserts is the particle size most capable of reaching the deep lung, and the particle size associated with optimal systemic absorption. However, the relative difference in fine particle dose for the 1 mg blister vs the 3 mg blister does not entirely account for the dose nonequivalence, as demonstrated in the following table proposed by the applicant for inclusion in the product label:

Table 5.1.2 Emitted Mass and Fine Particle Dose

Fill Mass (mg powder)	Nominal Dose (mg insulin)	Emitted Mass[1] (mg powder)	Fine Particle Dose[2] (mg insulin)
1.7	1.0	1.0	0.4
5.1	3.0	3.5	1.0

[1] Flow rate of 30 L/min for 2.5 seconds
[2] Flow rate of 28.3 L/min for 3 seconds

Source: Applicant's Table 1, proposed Exubera® label

The applicant has proposed some dose acceptance criteria using fine particle dose rather than emitted mass. This does not have a precedent within inhaled medicines. However, if further pharmacodynamic studies demonstrated a more consistent relationship between fine particle mass and pharmacodynamic effect, dose titration (and perhaps blister labeling) by fine particle mass might make dose titration less confusing. A crude indication of this was gained in Study 019, in which glucose pharmacodynamics were compared using 3.4 μM and 2.2 μM mean particle sizes. In this study, 2.2 μM particles resulted in higher AUC and Cmax than did and equivalent mass of 3.4 μM particles. Of possible use would be a comparison of rates of hypoglycemia and mean changes in glucose levels when one uses titration by mg dosing vs fine particle dosing.

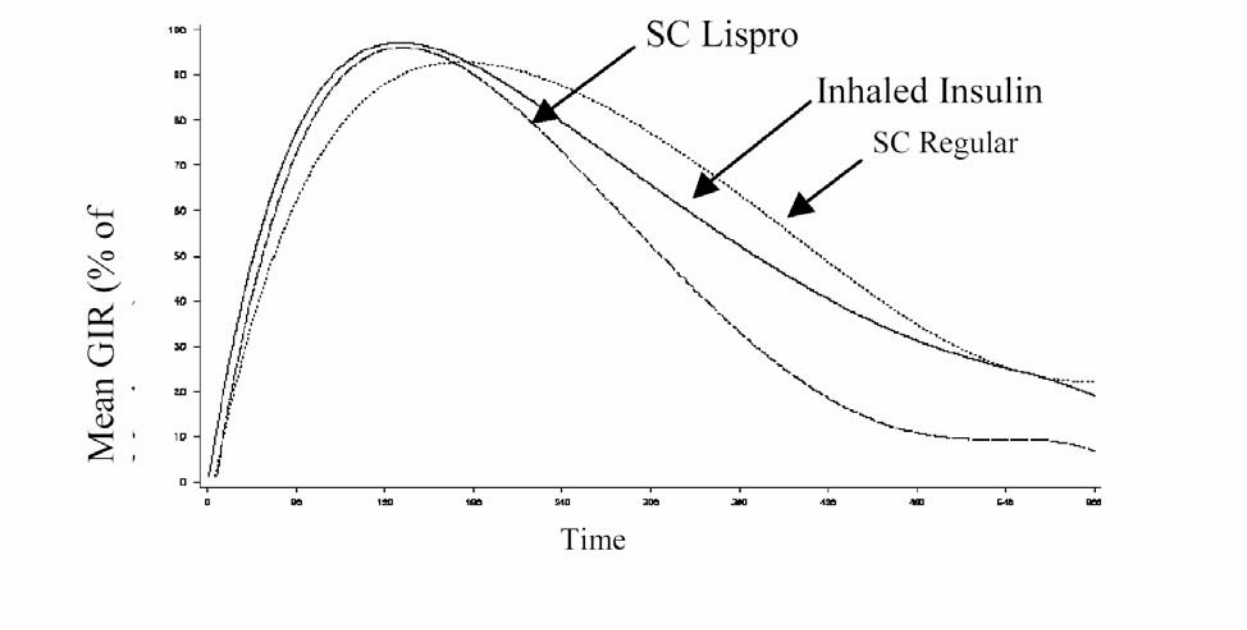
In addition to the potential problems noted above with titration, patients must be instructed not to substitute three 1 mg inhalations for one 3 mg inhalation if they run out of their 3 mg blisters. This could result in greater insulin exposure and risk for hypoglycemia.

As mentioned above, the FDA Biopharmacology review is ongoing as of 4 Aug 05; the material above is based on the clinical reviewer's examination of the NDA materials. However, the FDA Biopharmacology reviewer has the expertise in this area, and that review will represent the most accurate interpretation of the clinical pharmacology data.

5.2 Pharmacodynamics

In healthy subjects, inhaled insulin exhibited a rapid onset of action similar to SQ insulin lispro, and a duration of action similar to SQ regular insulin. This time-action profile is illustrated in the following figure from Study 217-017, a glucose clamp study. In this study, glucose was held nearly constant to a pre-defined level by varying the glucose infusion rate (GIR). An earlier GIR Tmax was demonstrated for inhaled insulin and SQ lispro than that seen for SQ regular insulin. A longer duration of action was demonstrated for inhaled insulin and SQ regular than for SQ lispro.

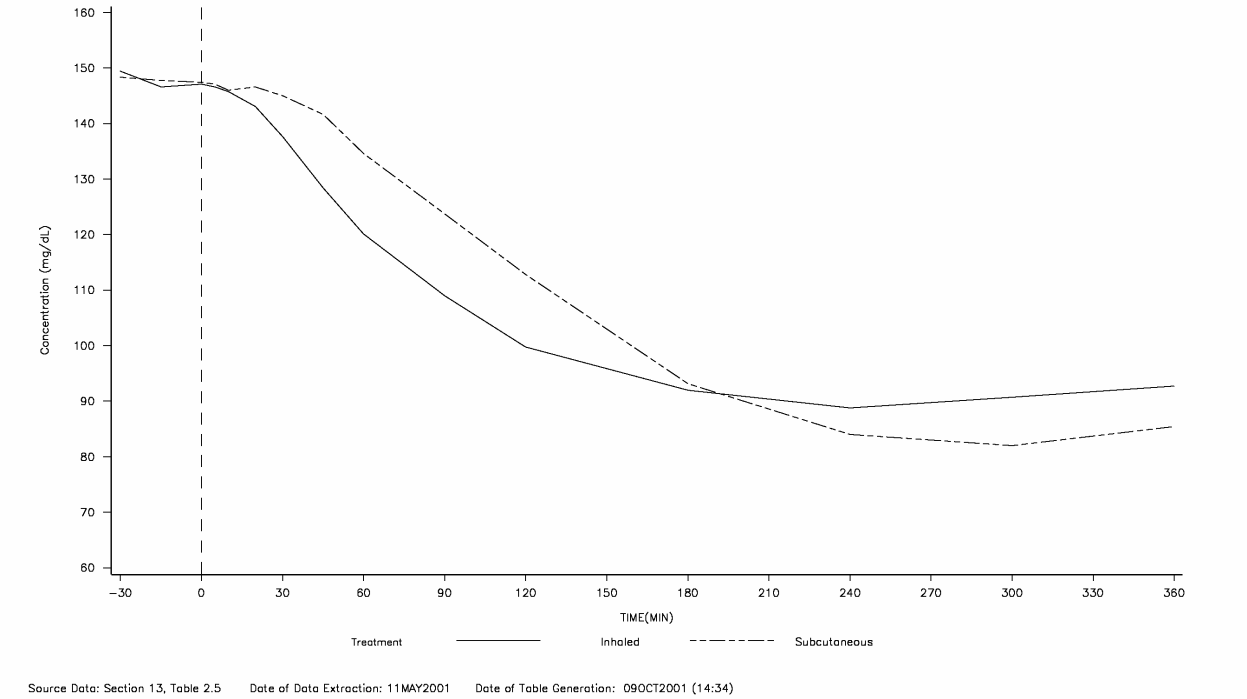
Figure 5.2.1 Mean Glucose Infusion Rate Over Time, Glucose Clamp Study 217-017, Healthy Subjects



Source: Module 2.7.2, Figure 8

Glucose clamp pharmacodynamics were not compared between insulin lispro and inhaled insulin in diabetic patients. In Study 1004, postprandial glucose declined somewhat more rapidly over the first 120 minutes after inhaled insulin administration than it did after SQ regular insulin administration. Time to peak glucose-lowering activity was not statistically significantly different between the two treatments.

Figure 5.2.2 Mean Glucose Concentration Following Administration of Inhaled Insulin (4 mg) or SQ Regular Insulin (12 U), Type 2 Diabetics, Study 1004



Source: Applicant's Figure 2.1, Study 1004 report

5.3 Exposure-Response Relationships

The applicant did not provide exposure-response analyses. Exposure-response relationships will be explored by the Biopharmaceutics reviewer.

6 INTEGRATED REVIEW OF EFFICACY

The applicant proposes the following language for the "Indications and Usage" section of the product label:

"EXUBERA is indicated for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia. EXUBERA has an onset of action similar to rapid-acting insulin analogs and has a duration of glucose-lowering activity comparable to subcutaneously administered regular human insulin. In patients with Type 1 diabetes, EXUBERA should be used in regimens that include a longer-acting insulin. In patients with type 2 diabetes, EXUBERA can be used as monotherapy or in combination with oral agents or longer-acting insulins."

Although the basic indication is for control of hyperglycemia in adult diabetics, the clinical reviewer chose to examine the evidence for efficacy for adult Type 1 and adult Type 2 diabetes separately, as these diseases differ in several ways, including etiology, age at onset, expected time from diagnosis to onset of complications, et al. Efficacy in adult Type 1 diabetics is

discussed in Section 6.1, and efficacy for adult Type 2 diabetics is discussed in Sections 6.2-6.4. Because the applicant proposes use in Type 2 diabetics either as monotherapy, or in combination with longer-acting insulins or oral agents, the clinical reviewer considered monotherapy and combination therapy trials separately. Section 6.2 covers inhaled insulin as monotherapy in Type 2 diabetes, Section 6.3 covers combined therapy for Type 2 diabetes with inhaled insulin and longer-acting insulins, and Section 6.4 covers combination therapy with inhaled insulin and oral agents.

Although the applicant does not seek an indication for the treatment of diabetes in pediatric patients, the clinical reviewer anticipates significant interest in the potential efficacy of this product in children, with the potential for widespread off-label use. The clinical reviewer therefore provides a brief review of the limited data regarding pediatric efficacy in Section 6.5.

For each of these indications, the clinical reviewer has provided specific review of the most relevant trial or trials for that indication. When appropriate, summary information for other trials regarding that indication has also been included.

6.1 Indication: Treatment of Hyperglycemia in Adult Type 1 Diabetics; Inhaled Insulin in Combination with a Longer-Acting Insulin

6.1.1 Methods

The clinical reviewer placed emphasis on Studies 217-106 and 217-107 for evaluation of efficacy for Type 1 diabetics. The applicant also designated these trials as "pivotal". Study 217-106 was a trial involving 334 patients, and compared inhaled insulin to "conventional" subcutaneous insulin therapy. Study 217-107 involved 327 patients, and compared inhaled insulin to "intensive" subcutaneous insulin therapy. Because the standard of care for Type 1 diabetics is now intensive insulin therapy, greater emphasis was placed on Study 217-107.

6.1.2 General Discussion of Endpoints

For both Study 217-107 and Study 217-106, the primary efficacy endpoint was the change in HbA1c from baseline to week 24 of treatment. HbA1c is well-accepted as a surrogate endpoint for evidence of glycemic control in diabetes, and is the most commonly used primary endpoint in diabetes efficacy trials submitted to the FDA. Of possible endpoints that are measurable within the limitations of practical clinical trial sample size and duration, HbA1c is at present, the best available surrogate endpoint. However, as with most such markers, HbA1c is an imperfect surrogate. Problems exist with assay variability, biologic variability between individuals, and the question of utility as a predictor of diabetic complications. An ideal trial would use diabetic complications as endpoints, but the trial size and duration needed for use of such endpoints would be very large. There is some controversy about whether HbA1c is truly a good marker of the risk for complications of diabetes. However, the correlation of HbA1c with risk for the development of microvascular disease in Type 1 diabetics is well-established (Jeffcoate 2004), and thus HbA1c is a good surrogate endpoint for the trials of inhaled insulin in Type 1 diabetics.

6.1.3 Study Design

6.1.3.1 General Description of Study Design

The design for Study 217-107 is described in Section 6.1.3.1.1; a brief description of how Study 217-106 differed from 217-107 appears in Section 6.1.3.1.2.

6.1.3.1.1 Design of Study 217-107

Study 217-107 was a 6-month, block-allocated (within center), open-label, parallel group efficacy and safety trial intended to establish noninferiority of inhaled insulin to subcutaneous insulin, with the goal of "intensive" diabetes control in both treatment groups. A total of 162 patients were treated with premeal inhaled insulin and 165 patients were treated with premeal regular insulin. All patients received NPH insulin prebreakfast and pre-bed (hs). The study included male and female Type 1 diabetics, ages 12-65 years, with HbA1cs between 6 and 11% at entry.

The primary efficacy endpoint was change in HbA1c from baseline to week 24 of treatment. A noninferiority margin of 0.5% was specified.

Secondary efficacy endpoints included (full list pg 31 of study report):
- percentage of patients achieving acceptable glycemic control (HbA1c <7% and <8%) at 24 weeks
- change in fasting plasma glucose
- two-hour postprandial glucose and insulin increments following a standardized meal (baseline and week 24)
- body weight
- fasting lipids

In addition to routine safety monitoring and laboratory, special safety assessments included:
- incidence and severity of hypoglycemic events
- chest X-ray at screening and week 24
- insulin antibodies at screening and week 24
- spirometry at baseline, week 12 and week 24
- lung volume, diffusion capacity and oxygen saturation at baseline and week 24
- thoracic high resolution computerized tomography (HRCT) in a subset of patients at baseline and week 24

6.1.3.1.2 Design Differences between Studies 107 and 106

Study 106 design differed from Study 107 design in the following ways:
- The control in 106 was "conventional" subcutaneous insulin administration, meaning that patients received only two shots per day, a mixture of NPH and regular insulin administered before breakfast and supper.

- Secondary endpoints included the percentage of patients achieving a HbA1c <8%, but not the percentage achieving <7%.

6.1.3.2 Adequacy of Study Design with Reference to Code of Federal Regulations Description of "Adequate and Well-controlled Studies"

The characteristics of "adequate and well-controlled" studies are described in 21 CFR 314.126; an abbreviated description includes the following:

- There is a clear statement of the objectives of the investigation and a summary of the proposed or actual methods of analysis in the protocol for the study and in the report of its results.
- The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect. A placebo concurrent control is the first acceptable type of control recognized in the regulation; other types of controls are possible in certain circumstances.
- The method of selection of subjects provides adequate assurance that they have the disease or condition being studied.
- The method of assigning patients to treatment and control groups minimizes bias and is intended to assure the comparability of the groups with respect to pertinent variables such as age, sex, severity of disease, duration of disease and use of drugs or therapy other than the test drug.
- Adequate measures are taken to minimize bias on the part of the subjects, observers and analysts of the data.
- The methods of assessment of subjects' response are well-defined and reliable.
- There is an analysis of the results of the study adequate to assess the effects of the drug.

In general, the designs of Studies 106 and 107 are consistent with "adequate and well-controlled trials". One concern regarding trial design was the method of treatment assignment. Patients were assigned to their treatment groups by block allocation within center rather than by true randomization, and it may have been possible for an investigator to predict the treatment group assignment of the next patient in a block. The investigator could then have chosen a "better" patient if the investigator could predict that the next patient would go to the inhaled insulin group, or a "worse" patient to go to the SQ group. However, statistical analyses did not reveal evidence of bias related to this treatment allocation method. The statistical review will include further explanation of the allocation procedure, and its implications.

All studies were open label, and none used inhaler or injection placebos. Historically, clinical trials of insulin have generally not been blinded trials, due to safety, logistical, and ethical concerns. In the case of Exubera, the use of a "double dummy" technique, where all patients had both an inhaler and injections (with only one of the two methods delivering active study drug or active control), would have been logistically very difficult and cumbersome. Placebo injections pose ethical issues, and Institutional Review Boards responsible for approval of initiation of trials often will not agree to allow studies to include placebo injections. Overall, the clinical reviewer generally did not note evidence of problems related to lack of blinding in Studies 106

and 107, or to lack of blinding in other Phase 2 and Phase 3 trials. However, please refer to Section 7.1.3 for a discussion of a concern for apparent misclassification of reasons for discontinuation. Apparent misclassification occurred more frequently among inhaled insulin group patients than among comparator patients. This discrepancy is unexplained, but may be attributable to investigator reporting bias in favor of open-label inhaled insulin.

6.1.4 Efficacy Findings

6.1.4.1 Demographics

Demographic characteristics for Studies 106 and 107 are included in the following table:

Table 6.1.4.1 Baseline Demographic and Clinical Characteristics of Patients in Studies 106 and 107

Characteristic	Inh Ins	SQ
Study 107 Male:Female	54:49	59:46
Study 106 Male:Female	70:67	71:64
Study 107 Mean Age, years	38.1	38.6
Study 106 Mean Age, years	38.2	38.2
Study 107 Mean BMI (with range), Male	26.1 (19-32)	26.3 (20-35)
Study 106 Mean BMI (with range), Male	26.4 (21-36)	25.8 (19-32)
Study 107 Mean BMI (with range), Female	24.7 (18-32)	24.9 (17-31)
Study 106 Mean BMI (with range), Female	25.1 (19-34)	25.2 (18-33)
Study 107 Race (White/Black/Asian/Hispanic/Other)	90/3/4/5/1	99/0/0/4/2
Study 106 Race (White/Black/Asian/Hispanic/Other)	121/5/2/9/0	128/2/0/3/2
Study 107 Mean Baseline HbA1c	8.12	8.16
Study 106 Mean Baseline HbA1c	8.23	8.24
Study 107 Mean Duration of Diabetes (range)	17.1 (2.2-50.0)	19.4 (1.5-49.0)
Study 106 Mean Duration of Diabetes (range)	19.0 (1.0-41.0)	18.5 (1.0-49.0)

Source: Applicant's Tables 7.1.1, 7.1.2, 7.2.1, 7.2.2, 7.4.1, 7.4.2, Module 2.7.3

Little difference was noted between groups for these demographic characteristics; few non-white patients participated.

6.1.4.2 Primary Endpoint

In both Studies 107 and 106, the inhaled insulin regimen was noninferior to the subcutaneous control regimen for the percent change in HbA1c from baseline to Week 24 of treatment. These results for Study 107 are illustrated in the following table:

Table 6.1.4.2.1 Mean Percent Change from Baseline in HbA1c to Week 24, Intention to Treat (ITT) Population, Study 107 (Control = "Intensive" SQ)

	Inh Ins (n = 162)		SQ (n = 162)	
	Mean	SD[1]	Mean	SD[1]
Baseline HbA1c	8.0	0.9	8	1.0
Week 24 (LOCF)[2]	7.7	1.0	7.8	1.2
Unadjusted change from baseline	-0.3	0.8	-0.1	0.9
Adjusted change from baseline[3]	-0.3	0.1	-0.1	0.1

1 SE used instead of SD for adjusted change from baseline

Table 6.1.4.2.1 Mean Percent Change from Baseline in HbA1c to Week 24, Intention to Treat (ITT) Population, Study 107 (Control = "Intensive" SQ)

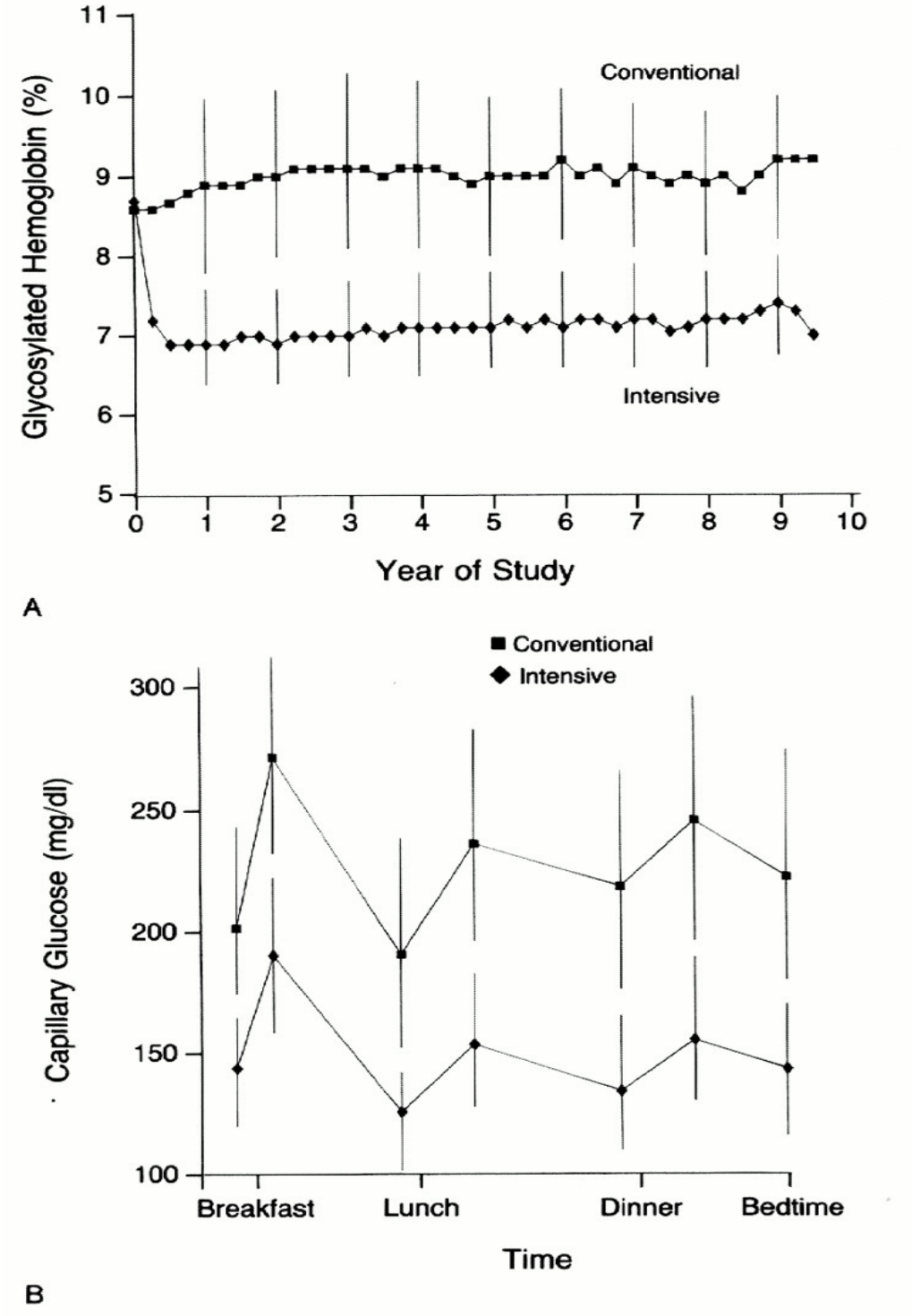
	Inh Ins (n = 162)		SQ (n = 162)	
	Mean	SD[1]	Mean	SD[1]

2 Last observation carried forward
3 Least Squares Means
Source: Applicant's Table 5.2.1, Study 107 Report, pg 139

For the treatment comparison, the difference between the adjusted mean changes from baseline for inhaled insulin vs SQ was - 0.17 (SE 0.09; 95% CI limits -0.34, 0.01).

During the development of Exubera®, DMEDP had communicated to the sponsor that, in their intensive control study, it was important that the subcutaneous control group actually achieve intensive control. Mean HbA1c in the DCCT at two years was slightly below 7% in the intensive control arm, and slightly below 9% in the conventional control arm, as illustrated in the following figure:

Figure 6.1.4.2 Mean HbA1c over Time in the Diabetes Control and Complications Trial



Source: DCCT Research Group 1993 (see reference section)

The following table displays the changes in HbA1c seen in Study 106. As in Study 107, the inhaled insulin was noninferior to subcutaneous insulin for change in HbA1c.

Table 6.1.4.2.2 Mean Percent Change from Baseline in HbA1c to Week 24, Intention to Treat (ITT) Population, Study 106 (Control = "Conventional" SQ)

	Inh Ins (n = 169)		SQ (n = 161)	
	Mean	**SD[1]**	**Mean**	**SD[1]**
Baseline HbA1c	8.1	1.0	8.1	1.0
Week 24 (LOCF)[2]	7.9	1.1	7.7	0.9
Unadjusted change from baseline	-0.2	0.9	-0.4	0.7
Adjusted change from baseline[3]	-0.2	0.1	-0.4	0.1

1 SE used instead of SD for adjusted change from baseline
2 Last observation carried forward
3 Least Squares Means
Source: Applicant's Table 5.2.1, Study 106 Report, pg 122

For the treatment comparison, the difference between the adjusted mean changes from baseline for inhaled insulin vs SQ was 0.16 (SE 0.08; 95% CI limits 0.08, 0.33).

6.1.4.3 Important Secondary Endpoints

The applicant used only their "evaluable" ("per protocol") patient population (i.e. not the "Intent to Treat" population) for the applicant's secondary efficacy analyses. The per protocol population included patients who did not have a major violation of the inclusion or exclusion criteria, received at least half the protocol-required duration of treatment (12 out of 24 weeks for both Studies 107 and 106), and had at least one "evaluable" post-baseline HbA1c. An evaluable HbA1c was defined as having been preceded by a treatment duration of 75% or more of the elapsed time since the previous assessment.

6.1.4.3.1 Treatment to Goal

In Study 107, the percentages of patients achieving HbA1cs <8% and <7% were comparable between the inhaled and SQ insulin groups at Week 24.

Table 6.1.4.3.1.1 Percentages of Patients Achieving <8% or <7% HbA1c at Week 24, Applicant's "Evaluable"[1] Population, Study 107

End-of-Study HbA1c	Inh Ins (n = 159) % of Patients	SQ (n = 159) % of Patients	Odds Ratio[2]	95% CI for Odds Ratio
<8%	64.2	60.4	1.44	0.77, 2.69
<7%	23.3	22.0	1.53	0.75, 3.14

1 Defined as patients who did not have a major violation of the inclusion or exclusion criteria, received at least half the protocol-required duration of treatment (12 out of 24 weeks for both Studies 107 and 106), and had at least one "evaluable" post-baseline HbA1c. An evaluable HbA1c was defined as having been preceded by a treatment duration of 75% or more of the elapsed time since the previous assessment.
2 Inhaled/SQ adjusted odds ratio. Crude odds of reaching vs not reaching specified HbA1c with inhaled/ Crude odds of reaching vs not reaching specified HbA1c with SQ
Source: Applicant's Tables 5.3.1.2 and 5.3.2.2, p 141, Study 107 report

In Study 106, the percentages of patients achieving HbA1cs <8% and <7% were again comparable between the inhaled and SQ groups at Week 24. A lower percentage of patients in both groups achieved a HbA1c <7% in Study 106 than in Study 107; this is expected with the less intensive regimen used in Study 106.

Table 6.1.4.3.1.2 Percentages of Patients Achieving <8% or <7% HbA1c at Week 24, Applicant's "Evaluable"[1] Population, Study 106

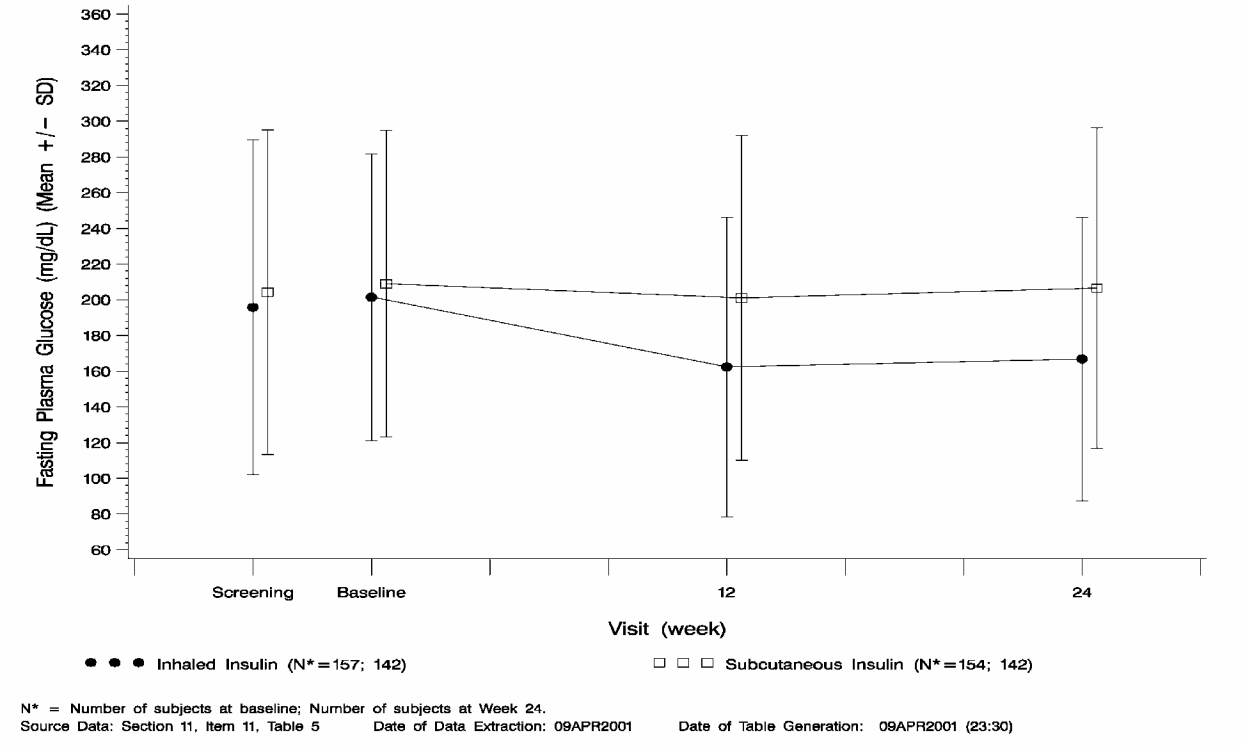
End-of-Study HbA1c	Inh Ins (n = 157) % of Patients	SQ (n = 155) % of Patients	Odds Ratio[2]	95% CI for Odds Ratio
<8%	58.0	61.9	0.71	0.39, 1.28
<7%	15.9	15.5	0.92	0.40, 2.10

1 Defined as patients who did not have a major violation of the inclusion or exclusion criteria, received at least half the protocol-required duration of treatment (12 out of 24 weeks for both Studies 107 and 106), and had at least one "evaluable" post-baseline HbA1c. An evaluable HbA1c was defined as having been preceded by a treatment duration of 75% or more of the elapsed time since the previous assessment.
2 Inhaled/SQ adjusted odds ratio. Crude odds of reaching vs not reaching specified HbA1c with inhaled/ Crude odds of reaching vs not reaching specified HbA1c with SQ
Source: Applicant's Tables 5.3.1.2 and 5.3.2.2, p 124, Study 106 report

6.1.4.3.2 Fasting Plasma Glucose

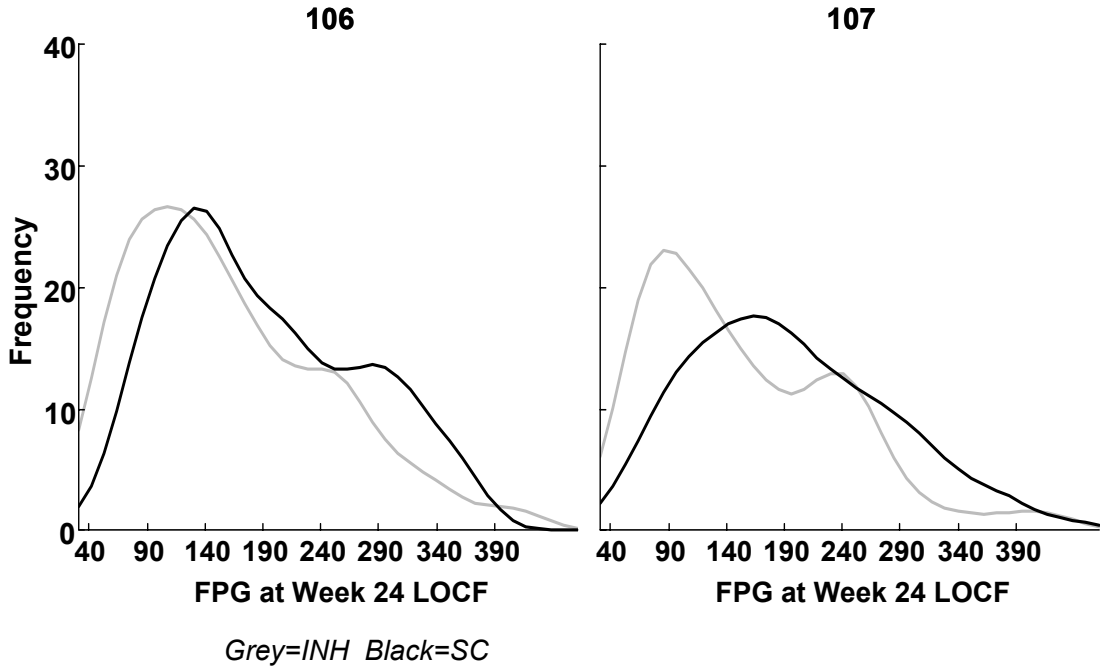
In Study 107, mean fasting plasma glucose concentrations were similar at baseline, but were significantly lower in inhaled insulin group patients than in SQ group patients at both week 12 and week 24. At week 24, inhaled insulin group patients had a mean decrease from baseline in fasting plasma glucose of 35 mg/dL, while patients in the SQ group had a mean increase of 4 mg/dL. The limits of the 95% confidence interval for the difference between groups were -57.50 and -21.56. This difference is illustrated in the following figure:

Figure 6.1.4.3.2.1 Fasting Plasma Glucose Over Time, Study 107, Per Protocol Population



Mean fasting plasma glucose in the SQ group did not fall in the desired range (<140 mg/dL after DCCT, 70 to <110 mg/dL by current standards of American Association of Clinical Endocrinologists). Frequency distribution for FPG values is illustrated in the following figures for Studies 106 and 107.

Figure 6.1.4.3.2.2 Distribution of Fasting Plasma Glucose Values, Studies 106 and 107



A higher percentage of Study 107 patients in the inhaled insulin group had a fasting blood sugar in the desired range than did patients in the SQ group. However, a higher percentage of patients in the inhaled insulin group also had fasting blood sugars below 70 mg/dL, which may be undesirably low. These differences are illustrated in the following table.

Table 6.1.4.3.2.1 Frequency of Fasting Plasma Glucose Below, Within, and Above the Desired Range, Week 24, Study 107

	<70 mg/dL # pts (%)	70-110 mg/dL # pts (%)	>110 mg/dL # pts (%)
Inhaled Insulin	10 (9.9)	29 (28.7)	62 (61.4)
SQ	4 (4.1)	12 (12.4)	81 (83.5)

Cochran-Mantel-Haenszel general association value 12.0078, p 0.0025
Source: analysis by Dr. Mele, FDA Biostatistics

The reason for the difference between groups for Study 107 is not clear. Concern exists for a lower intensity of management of SQ patients compared to inhaled insulin patients, which could limit the usefulness of Study 107 in determining whether inhaled insulin is noninferior to intensive SQ management. However, rules for titration of long-acting insulin were the same for both groups, and mean doses of both total daily and evening long-acting insulin were not higher for inhaled insulin patients than for SQ patients between groups; in fact, they were slightly higher for SQ group patients. Mean HbA1cs did not differ. As discussed in Section 7.1.3, hypoglycemia tended to occur more frequently in the prebreakfast time period than at other times of day for Type 1 inhaled insulin group patients. Logically, one would expect this finding, and that of lower fasting plasma glucoses in general, to be related to long-acting rather than short-acting insulin, but mean doses of long-acting insulin were not higher for inhaled insulin group

patients. The possibility was considered that subcutaneous group patients actually had more early morning hypoglycemia, with release of counterregulatory hormones and subsequent prebreakfast hyperglycemia (the "Somogyi effect"). However, routine early morning (0200 or 0300) blood sugars were not obtained during Study 107, and therefore this possibility could not be evaluated for this study. In Study 1026, the only study in which 0200 blood sugars were routinely monitored, hypoglycemia at 0200 was more common among inhaled insulin group patients than among SQ group patients. The clinical reviewer considered the possibility of an effect of inhaled insulin on reduction of nighttime hepatic glucose production, but was unable to examine this possibility with the data provided.

In Study 106, as in Study 107, a higher percentage of patients in the inhaled insulin group had fasting plasma glucoses <70 mg/dL at week 24 than did patients in the SQ group [17/131 (12.98%) for inh ins vs 1/129 (0.8%) for SQ]. End-of-study FPG was also lower in the inhaled insulin group than in the SQ group (adjusted difference -26.58; 95% CI -47.13, -6.02).

6.1.4.3.3 Postprandial Glucose Excursion

In Study 107, postprandial glucose excursions after a standard meal were greater at Week 24 for inhaled insulin patients than for SQ patients, as illustrated in the following table:

Table 6.1.4.3.3 Meal Study Postprandial Glucose Increment[1], Study 107, Per Protocol Set

	Inh Ins (n = 130) Mean Plasma Glucose mg/dL (SD) [2]	**SQ (n = 125) Mean Plasma Glucose mg/dL (SD) [2]**
Baseline	107 (96)	100 (95)
Week 24 (LOCF)	123 (100)	97 (101)
Unadjusted change from baseline	15 (107)	-3 (95)
Adjusted change from baseline[3]	17 (8)	-7 (8)
Treatment Comparison for Inhaled-Subcutaneous: Difference Between Adjusted Mean Change = 24.04; SE 11.18; 95% CI limits for difference 2.02, 46.07		
1 2-hour postprandial plasma glucose concentration minus preprandial (-30 min) value 2 SE used for adjusted change from baseline estimates 3 Least Squares Means based on primary model with terms for baseline, treatment and center		

In Study 107, inhaled insulin was somewhat less effective than SQ insulin in controlling postprandial glucose excursion. This difference likely contributes to the finding of similar HbA1cs between groups despite lower FPG with inhaled insulin. There is considerable debate in the medical literature about the relative importance of fasting vs postprandial glucose as targets of diabetes therapy. Randomized trials have not answered this question. In epidemiologic studies, postprandial glucose appears to be an independent risk factor for cardiovascular disease, and postprandial glucose may be a stronger risk factor for cardiovascular disease than FPG or HbA1c (Beisswenger 2004).

In Study 106, there was little difference between groups for postprandial glucose excursion.

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

In Study 107, a trial in Type 1 diabetics comparing management with preprandial inhaled insulin to management with subcutaneous insulin in an "intensive" manner, inhaled insulin was noninferior to subcutaneous insulin with regard to the primary endpoint, change from baseline in HbA1c. Inhaled insulin was associated with significantly lower fasting plasma glucose at end-of-study than was subcutaneous insulin, but more patients on inhaled insulin had undesirably low fasting plasma glucoses, also. This observation was not due to differences in evening longacting insulin doses. Postprandial glucose excursion was moderately numerically and statistically significantly greater in inhaled insulin group patients than in subcutaneous group patients, which is undesirable due to an epidemiologic association of postprandial glucose levels with cardiovascular risk. Indices of intensive control in Study 107 in the subcutaneous group were somewhat less "tight" than those seen in the "intensive" group in the Diabetes Control and Complications Trial, but were "tighter" than those for the "conventional" arm of the DCCT. Noninferiority of the inhaled insulin regimen to the subcutaneous regimen in this trial does not necessarily indicate noninferiority of this inhaled regimen to the intensive subcutaneous regimen used in the DCCT. However, 23% of patients in the inhaled insulin group were able to achieve a HbA1c of <7%, indicating that it is possible for tight control to be achieved in some patients using this inhaled insulin regimen.

By the best-validated surrogate endpoint available (HbA1c), intensive control of Type 1 diabetes appears possible for some patients with inhaled insulin. Special attention may be needed to ensure control of postprandial glucose excursion, and to avoid fasting hypoglycemia.

6.2 Indication: Treatment of Hyperglycemia in Adult Type 2 Diabetics, Inhaled Insulin as Monotherapy

6.2.1 Methods

Two major trials in Type 2 diabetics included an inhaled insulin monotherapy arm compared to oral agent(s). Study 109 enrolled patients who were poorly controlled on combination oral agent therapy, and randomized patients to one of three arms: premeal inhaled insulin monotherapy, premeal inhaled insulin plus the patient's baseline oral agents, or continued combination oral agents. Study 110 compared premeal inhaled insulin monotherapy to rosiglitazone treatment.

6.2.2 General Discussion of Endpoints

For Study 109, the primary efficacy endpoint was the change in HbA1c from baseline at week 12. For Study 110, the primary efficacy endpoint was the percentage of patients achieving a HbA1c <8% by the end-of-study or discontinuation.

As discussed in Section 6.1.2, the correlation of HbA1c with the development of microvascular disease in Type 1 diabetics is well-established, and thus HbA1c is a good surrogate endpoint for the trials of inhaled insulin in Type 1 diabetics. However, the evidence that monitoring of HbA1c is of value in predicting or preventing macrovascular disease in Type 2 subjects is less strong than that for microvascular disease in Type 1 diabetics (Jeffcoate 2004). HbA1c remains, however, the best-validated surrogate endpoint for diabetes trials in Type 2 patients.

6.2.3 Study Design

6.2.3.1 Design of Study 109

Study 109 was a 3-month, block-allocated, open-label, parallel group study done in patients who were already receiving combination oral antidiabetic agents, and who had entry HbA1cs ≥ 8% to ≤ 11%. All patients were on an insulin secretagogue (sulfonylurea or repaglinide) and another agent (either metformin or a glitazone). Patients were assigned to one of three treatment groups: continued oral therapy alone, premeal inhaled insulin monotherapy, or premeal inhaled insulin plus continued oral therapy. The objective was to see if inhaled insulin as monotherapy or in combination with continued oral agents would significantly improve HbA1c when compared to continued oral agent therapy alone. In this section regarding the applicant's proposed monotherapy indication, the monotherapy arm's effect relative to the "oral agent alone" arm will be considered. A total of 104 patients were treated with inhaled insulin monotherapy, while 99 continued oral agent therapy alone. The patient population included men and women ages 35-80 years who had been on a stable oral agent regimen (as described above) for at least two months.

The primary efficacy endpoint was the change in HbA1c from baseline at week 12.

Secondary efficacy endpoints included (full list p 25 study report):
- change in fasting plasma glucose
- percentage of patients with HbA1c <8% and <7%
- two-hour postprandial glucose and insulin increments following a standardized meal
- body weight
- fasting lipids

In addition to routine safety monitoring and laboratory, special safety assessments included:
- spirometry, lung volume, diffusion capacity and oxygen saturation at baseline and week 12
- incidence and severity of hypoglycemic events
- insulin antibodies at baseline and week 12

6.2.3.2 Design of Study 110

Study 110 was a 3-month, block-allocated, open-label, parallel group efficacy and safety study intended to establish superiority of premeal inhaled insulin monotherapy over rosiglitazone for the treatment of Type 2 diabetes. The population included Type 2 diabetics, ages 35-80

inclusive, who had not previously been on insulin, and who had HbA1cs ranging from 6-11%. A total of 75 patients were treated with inhaled insulin, and 68 were treated with rosiglitazone.

The primary efficacy endpoint was the percentage of patients achieving HbA1c <8% by the end of study or discontinuation.

Secondary efficacy endpoints included (full list pg 23 of study report):
- change from baseline to week 12 in HbA1c
- percentage of patients reaching HbA1c <7%
- change in fasting plasma glucose
- two-hour postprandial glucose increment after a standardized meal
- fasting lipids

Routine and special safety monitoring was the same as that used in Study 109.

6.2.3.3 Adequacy of Study Design

Please see Section 6.1.3.2 for a description of the regulatory definition of "adequate and well-controlled studies". Studies 109 and 110 have the same issues as Studies 106 and 107 with regard to blinding and randomization.

6.2.4 Efficacy Findings

6.2.4.1 Demographics

Demographic characteristics of patients in Studies 109 and 110 are included in the following table:

Table 6.2.4.1 Baseline Demographic and Clinical Characteristics of Patients in Studies 109 and 110

Characteristic	Inh Ins	OA
Study 109 Male:Female	75:30	62:37
Study 110 Male:Female	48:27	31:37
Study 109 Mean Age, years	57.4	56.4
Study 110 Mean Age, years	53.0	54.4
Study 109 Mean BMI (with range), Male	30.5 (22-39)	29.3 (23-38)
Study 110 Mean BMI (with range), Male	31.7 (24-43)	32.6 (24-46)
Study 109 Mean BMI (with range), Female	29.3 (24-39)	31.2 (18-37)
Study 110 Mean BMI (with range), Female	32.2 (20-44)	32.8 (22-48)
Study 109 Race (White/Black/Asian/Hispanic/Other)	83/8/2/8/4	82/5/2/7/3
Study 110 Race (White/Black/Asian/Hispanic/Other)	58/7/1/9/0	48/10/0/9/1
Study 109 Mean Baseline HbA1c	9.58	9.56
Study 110 Mean Baseline HbA1c	9.76	9.64
Study 109 Mean Duration of Diabetes (range)	9.3 (1.8-25.0)	9.6 (1.3-32.8)
Study 110 Mean Duration of Diabetes (range)	4.3 (0.08-22.0)	3.1 (0.01-18.0)
Source: Applicant's Tables 9 and 11, Section 2.7.3.3.1.2		

6.2.4.2 Study 109

6.2.4.2.1 Primary Endpoint

Inhaled insulin monotherapy was superior to continued oral agent therapy for change in HbA1c at Week 12, for this population that was failing oral agent therapy at baseline. HbA1c data are summarized in the following table:

Table 6.2.4.2.1 Mean Change from Baseline in HbA1c, Study 109, ITT Population

Group	N	BL	Wk 12	Adjusted Change[a]	Difference (Inh Grp vs OA)	95% CI Limits for Difference between Grps	p-Value
Inh Ins Monotherapy	102	9.3	7.9	-1.4	-1.18[b]	-1.41, -0.95	<0.0001[b]
Inh Ins + OA	100	9.2	7.3	-1.9	-1.67[c]	-1.90, -1.44	<0.0001[c]
OA	96	9.3	9.1	-0.2			

a Least Squares Means based on the primary model with terms for baseline, treatment and center
b Comparison of inh ins monotherapy to OA
c Comparison of inh ins + OA to OA
Source: Applicant's Table 5.2.1, p 42, Study 109 report

6.2.4.2.2 Secondary Endpoints

6.2.4.2.2.1 Treatment to Goal

Inhaled insulin monotherapy was superior to continued oral agent therapy for achievement of HbA1c <8% and <7%, for this population that was failing oral agent therapy at baseline.

Table 6.2.4.2.2.1 Percentage of Patients Achieving HbA1c <8% and <7%, Study 109, ITT Population

	N	Baseline # pts (%)	End-of-Study # pts (%)	Odds Ratio (Inh Ins Grp vs OA Grp)	95% CI Limits for Odds Ratio
<8%					
Inh Ins Monotherapy	102	3 (2.9)	57 (55.9)	7.5	3.6, 15.5
Inh Ins + OA	100	5 (5.0)	86 (86.0)	40.5	17.0, 96.9
OA	96	3 (3.1)	18 (18.8)		
<7%					
Inh Ins Monotherapy	102	0	17 (16.7)	19.0	2.5, 145.8
Inh + OA	100	0	32 (32.0)	44.7	6.0, 335.2
OA	96	0	1 (1.0)		

Source: Applicant's Tables 5.3.1.1 and 5.3.2.1, Study 109 report

6.2.4.2.2.2 Fasting and Postprandial Glucose

Inhaled insulin monotherapy was superior to continued oral agent therapy in reduction of fasting plasma glucose and postprandial glucose excursion in this population that was failing oral agent therapy.

Table 6.2.4.2.2.2 Mean Fasting Plasma Glucose and Mean Postprandial Glucose Excursion, Study 109, Per Protocol Population

		n	BL	Wk 12 Change	Difference between Inh Ins Grp and OA Grp	95% CI Limits for Difference between Grps
FPG						
	Inh Ins Monotherapy	95	203	-23	-24	-36, -11
	Inh Ins + OA	96	195	-53	-53	-66, -41
	OA	89	203	1		
Two-hour Postprandial Glucose Change (from Preprandial Value)						
	Inh Ins Monotherapy	91	98	-43	-41	-56, -25
	Inh Ins + OA	91	95	-24	-22	-37, -7
	OA	79	95	-2		

Source: Applicant's Tables 5.6.1 and 5.6.3, Study 109 report

6.2.4.3 Study 110

6.2.4.3.1 Primary Endpoint-Treatment to Goal

Inhaled insulin monotherapy was superior to rosiglitazone for the primary endpoint, percentage of patients achieving a HbA1c <8%. A higher percentage of patients in the inhaled insulin group also achieved a HbA1c <7%.

Table 6.2.4.3.1 Percentage of Patients Achieving HbA1cs <8% and <7%, Study 110, ITT Population

	N	End-of Study Patients to HbA1c Goal # pts (%)	Odds Ratio (Inh Ins Grp vs Rosi Grp)	95% CI Limits for Odds Ratio	p Value
<8%					
Inh Ins Monotherapy	75	62 (82.7)	7.14	2.48, 20.58	0.0003
Rosi	67	39 (58.2)			
<7%					
Inh Ins Monotherapy	75	33 (44.0)	4.43	1.94, 10.12	
Rosi	67	12 (17.9)			

Source: Applicant's Tables 5.3.1.1 and 5.3.2.1, Study 110 report

6.2.4.3.2 Secondary Endpoints

6.2.4.3.2.1 Change from Baseline in HbA1c

Inhaled insulin treatment resulted in a greater decline in HbA1c than that seen with rosiglitazone.

Table 6.2.4.3.2.1 Mean Change from Baseline in HbA1c, Study 110, ITT Population

Group	N	BL HbA1c (SD)	Wk 12 HbA1c (SD)	Adjusted Change[a]	Difference (Inh Grp vs Rosi)	95% CI Limits for Difference between Grps
Inh Ins Monotherapy	75	9.5 (1.1)	7.2 (1.0)	-2.3 (1.2)	-0.89	-1.23, -0.55
Rosi	67	9.4 (0.9)	8.0 (1.3)	-1.4 (1.2)		

Source: Applicant's Table 5.2.1, Study 110 report
a Least Squares Means based on the primary model with terms for baseline, treatment and center

6.2.4.3.2.2 Fasting and Postprandial Plasma Glucose

The difference between groups was not significant for change from baseline in FPG and postprandial glucose excursion.

Table 6.2.4.3.2.2 Mean Fasting Plasma Glucose and Mean Postprandial Glucose Excursion, Study 110, Per Protocol Population

		n	BL (SD)	Wk 12 Change (SD)	Difference between Inh Ins Grp and OA Grp	95% CI Limits for Difference between Grps
FPG						
	Inh Ins Monotherapy	68	208 (56)	-64 (57)	-4.26	-17.66, 9.13
	Rosi	57	199 (50)	-56 (42)		
Two-hour Postprandial Glucose Change (from Preprandial Value)						
	Inh Ins Monotherapy	63	86 (49)	-27 (48)	14.12	-4.25, 32.49
	Rosi	54	82 (56)	-38 (60)		

Source: Applicant's Table 5.6.3, Study 110 report

6.2.5 Clinical Microbiology

Not applicable.

6.2.6 Efficacy Conclusions

From Study 109, it appears that inhaled insulin monotherapy is effective in achieving better glucose control (by HbA1c) for Type 2 patients who are failing combination oral agent therapy. From Study 110, inhaled insulin monotherapy appears superior to rosiglitazone in achieving HbA1c goals in Type 2 patients not previously exposed to injected insulin.

6.3 Indication: Treatment of Hyperglycemia in Adult Type 2 Diabetics, Inhaled Insulin in Combination with Longer-acting Insulins

6.3.1 Methods

Study 108 was the major completed trial utilizing inhaled insulin in combination with a longer-acting insulin for Type 2 diabetics, and review focused on this study.

6.3.2 General Discussion of Endpoints

The primary efficacy endpoint was the change in HbA1c from baseline to week 24 of treatment. Please see Sections 6.1.2 and 6.2.2 for a discussion of the value of HbA1c as an endpoint in trials in Type 1 and Type 2 diabetes.

6.3.3 Study Design

Study 108 was a 6 month, block-allocated, open-label, parallel group study done in Type 2 patients who had been on a stable regimen of SQ insulin for at least 2 months prior to study entry, and who had entry HbA1cs between 8 and 11%. Patients were assigned to receive either TID premeal inhaled insulin plus bedtime Ultralente® (UL), or BID mixed SQ NPH and regular insulin. The objective was to determine if inhaled insulin administered in this regimen was at least as effective (in control of HbA1c) as BID mixed SQ insulin. Each arm contained 149 treated patients.

The primary efficacy endpoint was change in HbA1c from baseline to week 24. Secondary endpoints and special safety assessments were similar to those described previously for Study 109.

Please see Section 6.1.3.2 for a discussion of the regulatory characteristics of "adequate and well-controlled" studies. Study 108 has the same concerns with patient assignment by block allocation within center as previously described for other studies. The clinical reviewer had some concern regarding the lower intensity of management in the SQ group (two insulin doses per day) compared to the inhaled insulin group (four insulin doses per day). The increased attention to self-care required for a four time per day intervention might in itself result in a greater decrease in HbA1c than one could achieve with a twice daily intervention. However, a twice daily injected insulin regimen is commonly used in Type 2 diabetes, and thus permits comparison to "usual care". Likely clinical scenarios of use for inhaled insulin in Type 2 diabetics would be either one in which the patient is on a mixed BID regimen and wishes to take fewer injections per day, or one in which the clinician or patient desires tighter control, but wishes to spare the patient a four shot per day regimen. In these cases, substitution of a TID premeal inhaled insulin plus a q day basal SQ injection would be likely. It will be important in this scenario to know if one would be putting the patient at risk of more hypoglycemic episodes in general, or of more serious hypoglycemic episodes. This trial design permits exploration both of the efficacy of this premeal inhaled + q day basal SQ regimen, and of the safety of the regimen with regard to the possibility of increased hypoglycemia. Furthermore, it appears that the likely efficacy of the inhaled insulin portion of this regimen is not in question, because in Study 109 (see Section 6.2.4), inhaled insulin monotherapy was effective in improving glycemic control in Type 2 diabetics who were failing dual oral agent therapy.

6.3.4 Efficacy Findings

6.3.4.1 Demographics

Table 6.3.4.1 Baseline Demographic and Clinical Characteristics of Patients in Study 108

Characteristic	Inh Ins	OA
Male:Female	99:50	99:50
Mean Age, years	58.7	56.2
Mean BMI (with range), Male	29.9 (21-38)	29.5 (21-38)
Mean BMI (with range), Female	31.7 (22-51)	31.1 (22-38)
Race (White/Black/Asian/Hispanic/Other)	116/17/4/11/1	110/15/5/12/17
Mean Baseline HbA1c	8.48	8.47 (0.4-59.0)
Mean Duration of Diabetes (range)	13.8	13.2 (0.9-43.4)

Source: Applicant's Tables 9 and 11, Section 2.7.3.3.1.2

Little difference was noted between groups for these characteristics.

6.3.4.2 Primary Endpoint

For change from baseline in HbA1c, the inhaled insulin plus hs UL regimen was noninferior to the BID mixed SQ regimen.

Table 6.3.4.2 Mean Change from Baseline in HbA1c, Study 108, ITT Population

Group	N	BL (SD)	Wk 24 (SD)	Adjusted Change[a] (SD)	Difference (Inh Grp vs SQ)	95% CI Limits for Difference between Grps	p-Value
TID premeal Inh Ins + hs UL	146	8.1 (1.1)	7.4 (1.5)	-0.7 (1.2)	-0.07	-0.31, 0.17	NS
BID SQ mixed NPH and regular insulin	149	8.2 (1.1)	7.6 (1.1)	-0.6 (1.1)			

a Least Squares Means based on the primary model with terms for baseline, treatment and center
Source: Applicant's Table 5.2.1, Study 108 report

6.3.4.3 Secondary Efficacy Endpoints

6.3.4.3.1 Treatment to Goal

A slightly higher percentage of patients in the inhaled insulin +basal SQ group achieved HbA1cs of <8% and <7% than did patients in the BID SQ group.

Table 6.3.4.3.1 Percentage of Patients Achieving HbA1c <8% and <7%, Study 108, ITT Population

	N	BL # pts (%)	End-of Study # pts (%)	Odds Ratio (Inh Ins Grp vs OA Grp)	95% CI Limits for Odds Ratio
<8%					
TID premeal Inh Ins + hs UL	146	70 (47.9%)	111 (76.0%)	1.58	0.82, 3.06
BID SQ mixed NPH and regular insulin	149	68 (45.6%)	103 (69.1%)		

Table 6.3.4.3.1 Percentage of Patients Achieving HbA1c <8% and <7%, Study 108, ITT Population

	N	BL # pts (%)	End-of Study # pts (%)	Odds Ratio (Inh Ins Grp vs OA Grp)	95% CI Limits for Odds Ratio
<7%					
TID premeal Inh Ins + hs UL	146	25 (17.5%)	66 (45.2)	1.92	1.07, 3.44
BID SQ mixed NPH and regular insulin	149	17 (11.7%)	48 (32.2)		

Source: Applicant's Table 22, NDA Section 2.7.3.3.2.2.2; Tables 5.3.1.2 and 5.3.2.2, Study 108 report

6.3.4.3.2 Fasting and Postprandial Plasma Glucose

Fasting plasma glucose declined more in inhaled insulin group patients; there was no significant difference between groups in the change in postprandial glucose increment.

Table 6.3.4.3.2 Mean Fasting Plasma Glucose and Mean Postprandial Glucose Excursion, Study 108, ITT Population

	n	BL (SD)	Wk 24 Change (SD)	Difference between Inh Ins Grp and SQ Grp	95% CI Limits for Difference between Grps
FPG					
TID premeal Inh Ins + hs UL	144	152 (37)	-20 (55)	-16.36	-27.09, -5.63
BID SQ mixed NPH and regular insulin	144	159 (45)	-9 (52)		
Two-hour Postprandial Glucose Change (from Preprandial Value)					
TID premeal Inh Ins + hs UL	115	89 (47)	3 (6)	6.58	-8.79, 21.94
BID SQ mixed NPH and regular insulin	116	94 (83)	-4 (6)		

Source: Applicant's Tables 5.6.3, 5.6.1, Study 108 report

6.3.5 Clinical Microbiology

Not applicable.

6.3.6 Efficacy Conclusions

In Study 108, a regimen of TID premeal inhaled insulin plus bedtime UL was noninferior to a low-intensity regimen of BID SQ mixed regular and NPH insulin, for the control of HbA1c in Type 2 diabetics. It appears that Type 2 diabetics who have been on a subcutaneous insulin regimen can switch to a regimen of premeal inhaled insulin plus basal injected insulin, and achieve at least noninferior glycemic control without undue risk of increased or worsening hypoglycemia (see Section 7.1.3.3.1 for details regarding hypoglycemia rates) .

Addendum: The applicant provided an interim analysis of an ongoing study, Study 1029. In this study, patients in the inhaled insulin group are receiving TID premeal inhaled insulin plus hs intermediate to long-acting insulin (UL, NPH or glargine), and patients in the SQ group are receiving TID premeal insulin (regular, aspart or lispro) and hs intermediate to long-acting

insulin (UL, NPH or glargine). A one-year interim analysis of this study indicates noninferiority of the inhaled regimen(s) to the SQ regimen(s), with changes from baseline in HbA1c of -0.53 (SE 0.05) for the inhaled insulin group and -0.60 (SE 0.05) for the SQ group. The final results of this study will allow comparison of similar intensity regimens of inhaled and SQ premeal insulins in combination with basal SQ insulin.

6.4 Indication: Treatment of Hyperglycemia in Adult Type 2 Diabetics, Inhaled Insulin in Combination with Oral Agents

6.4.1 Methods

The applicant submitted the results of two major controlled trials in Type 2 diabetics in which inhaled insulin was administered in combination with an oral agent. Study 109, discussed above in Section 6.2, included an arm with TID premeal insulin plus continued combination oral hypoglycemic agents (insulin secretagogue, plus glitazone or metformin). Studies 1001 and 1002 began as separate trials, but were later combined. Study 1001 combined inhaled insulin with a sulfonylurea, and Study 1002 combined inhaled insulin with metformin.

6.4.2 General Discussion of Endpoints

For both Study 1001, and 1002, the primary endpoint was change from baseline in HbA1c. As discussed above in Section 6.1.2, the value of HbA1c as a surrogate for the risk of development of macrovascular disease in Type 2 diabetics is less well-established than the value of HbA1c as a surrogate for the risk of development of microvascular disease in Type 1 diabetics. However, at this time, HbA1c remains the best-validated surrogate for evaluation of the glucose-lowering efficacy of antidiabetic agents.

6.4.3 Study Designs

Both Study 1001 and Study 1002 were designed as 104 week studies, but at 24 weeks, the two studies were combined, and changes in design were included at that point. Therefore, only the data to 24 weeks are used in this efficacy evaluation.

Study 1001 was a block-allocated, open-label, parallel group study done in patients who were already poorly controlled on sulfonylurea therapy and had HbA1cs between 8 and 12%. HbA1c strata included 8-9.5, and >9.5-12. Patients were assigned to one of two groups: TID premeal inhaled insulin + continued SU, or metformin (1 gm BID) + continued SU. The objective was to demonstrate superiority of the inhaled insulin regimen over the metformin regimen for change in HbA1c for the high HbA1c stratum. A total of 222 patients were treated with inhaled insulin and 201 were treated with metformin.

Study 1002 was a block-allocated, open-label, parallel group study done in patients who were already poorly controlled on metformin (1 gm BID) and had HbA1cs between 8 and 12%. HbA1c strata included 8-9.5, and >9.5-12. Patients were assigned to one of two groups: TID

premeal inhaled insulin + continued metformin, or glibenclamide (maximum dose 5 mg BID) + continued metformin. The objective was to demonstrate superiority of the inhaled insulin regimen over the glibenclamide regimen for change in HbA1c for the high HbA1c stratum. A total of 235 patients received inhaled insulin and 229 received glibenclamide.

The primary efficacy endpoint for both studies was change from baseline in HbA1c, and both had similar secondary endpoints and special safety evaluations.

6.4.4 Efficacy Findings

6.4.4.1 Demographics

The following table lists baseline demographics and characteristics for the two studies.

Table 6.4.4.1 Baseline Demographic and Clinical Characteristics of Patients in Studies 1001 and 1002

Characteristic	Inh Ins + Continued SU (Study 1001) or Inh Ins + Continued Met (Study 1002)	Met + Continued SU (Study 1001) or Glibenclamide + Continued Met (Study 1002)
Study 1001 Male:Female (HbA1c 8-9.5)	52:53	49:44
Study 1001 Male:Female (HbA1c >9.5-12)	70:47	53:55
Study 1002 Male:Female (HbA1c 8-9.5)	74:56	79:47
Study 1002 Male:Female (HbA1c >9.5-12)	62:47	53:52
Study 1001Mean Age (HbA1c 8-9.5)	60.5	60.2
Study 1001Mean Age (HbA1c >9.5-12)	61.0	59.8
Study 1002 Mean Age (HbA1c 8-9.5)	56.2	56.3
Study 1002 Mean Age (HbA1c >9.5-12)	54.6	54.4
Study 1001 Mean BMI (with range), Male (HbA1c 8-9.5)	27.4 (20-34)	28.6 (21-44)
Study 1001 Mean BMI (with range), Male (HbA1c >9.5-12)	27.9 (22-41)	28.3 (20-37)
Study 1002 Mean BMI (with range), Male (HbA1c 8-9.5)	30.7 (19-51)	30.7 (24-44)
Study 1002 Mean BMI (with range), Male (HbA1c >9.5-12)	30.9 (22-47)	30.4 (23-38)
Study 1001 Mean BMI (with range), Female (HbA1c 8-9.5)	29.6 (23-40)	30.3 (21-42)
Study 1001 Mean BMI (with range), Female (HbA1c >9.5-12)	29.4 (22-48)	29.3 (21-57)
Study 1002 Mean BMI (with range), Female (HbA1c 8-9.5)	33.3 (21-47)	31.9 (22-45)
Study 1002 Mean BMI (with range), Female (HbA1c >9.5-12)	32.8 (23-43)	31.9 (22-47)
Study 1001 Race (White/Black/Asian/Other) (HbA1c 8-9.5)	102/3/0/0	91/1/0/1
Study 1001 Race (White/Black/Asian/Other) (HbA1c >9.5-12)	109/1/3/4	101/2/3/2
Study 1002 Race (White/Black/Asian/Other) (HbA1c 8-9.5)	123/1/5/1	120/2/3/1
Study 1002 Race (White/Black/Asian/Other) (HbA1c >9.5-12)	99/5/0/5	100/2/1/2
Study 1001 Mean Baseline HbA1c (HbA1c 8-9.5)	9.04	8.95
Study 1001 Mean Baseline HbA1c (HbA1c >9.5-12)	10.66	10.66
Study 1002 Mean Baseline HbA1c (HbA1c 8-9.5)	8.90	9.00
Study 1002 Mean Baseline HbA1c (HbA1c >9.5-12)	10.73	10.94

Table 6.4.4.1 Baseline Demographic and Clinical Characteristics of Patients in Studies 1001 and 1002

Characteristic	Inh Ins + Continued SU (Study 1001) or Inh Ins + Continued Met (Study 1002)	Met + Continued SU (Study 1001) or Glibenclamide + Continued Met (Study 1002)
Study 1001 Mean Duration of Diabetes, years (range) (HbA1c 8-9.5)	9.1 (0.7-28.3)	8.2 (0.5-20.7)
Study 1001 Mean Duration of Diabetes, years (range) (HbA1c >9.5-12)	10.1 (0.8-37.3)	9.2 (1.1-33.0)
Study 1002 Mean Duration of Diabetes, years (range) (HbA1c 8-9.5)	7.7 (0.6-30.3)	7.4 (0.3-27.5)
Study 1002 Mean Duration of Diabetes, years (range) (HbA1c >9.5-12)	9.2 (0.6-35.6)	8.4 (0.5-29.5)

Source: Applicant's Tables 9 and 11, Section 2.7.3.3.1.2

No clear differences in demographic characteristics exist between groups.

6.4.4.2 Primary Endpoints

For Study 1001, for change from baseline in HbA1c, inhaled insulin + SU was not superior to metformin + SU for patients with baseline HbA1cs between 8 and 9.5. For patients with HbA1cs between >9.5 and 12, inhaled insulin +SU was statistically superior to metformin + SU. However, the HbA1c difference between groups (-0.38; 95% CI -.63, -0.14) is of uncertain clinical significance for the treatment of Type 2 diabetes. The addition of inhaled insulin to failed sulfonylurea therapy does not appear to be inferior to the addition of metformin to failed sulfonylurea therapy for reduction in HbA1c.

Table 6.4.4.2.1 Mean Change from Baseline in HbA1c at 6 Months, Study 1001, ITT Population

Group	N	BL (SD)	Wk 24 (SD)	Adjusted Change[a] (SD)	Difference (Inh + Continued SU vs Met + Continued SU)	95% CI Limits for Difference between Grps	p-Value
Inh + Continued SU, Baseline HbA1c 8-9.5	101	8.8 (0.5)	7.4 (0.8)	-1.4 (0.8)	-0.07	-0.33, 0.19	0.610
Met + Continued SU, Baseline HbA1c 8-9.5	93	8.8 (0.5)	7.4 (0.8)	-1.4 (0.9)			
Inh + Continued SU, Baseline HbA1c >9.5-12	113	10.5 (0.7)	7.9 (1.0)	-2.7 (1.1)	-0.38	-0.63, -0.14	0.002
Met + Continued SU, Baseline HbA1c >9.5-12	103	10.6 (0.9)	8.3 (1.2)	-2.4 (1.2)			

a Least Squares Means based on the primary model with terms for baseline, treatment and center
Source: Applicant's Tables 5.2.1.2 and 5.2.1.3, Study 1001 report

For Study 1002, for change from baseline in HbA1c, inhaled insulin + continued metformin was not superior to glibenclamide + continued metformin for patients with baseline HbA1cs between 8 and 9.5. For patients with HbA1cs between >9.5 and 12, inhaled insulin + continued metformin was statistically superior to glibenclamide + continued metformin. However, the

HbA1c difference between groups (-0.37; 95% CI -.62, -0.12) is of uncertain clinical significance for the treatment of Type 2 diabetes. The addition of inhaled insulin to failed metformin therapy does not appear to be inferior to the addition of glibenclamide to failed metformin therapy for reduction in HbA1c.

Table 6.4.4.2.2 Mean Change from Baseline in HbA1c at 6 Months, Study 1002, ITT Population

Group	N	BL (SD)	Wk 24 (SD)	Adjusted Change[a] (SD)	Difference (Inh + Continued Met vs Glibenclamide + Continued Met)	95% CI Limits for Difference between Grps	p-Value
Inh + Continued Met, Baseline HbA1c 8-9.5	125	8.6 (0.5)	7.2 (0.8)	-1.4 (0.8)			
Glibenclamide + Continued Met, Baseline HbA1c 8-9.5	119	8.7 (0.5)	7.1 (0.9)	-1.6 (0.9)	0.04	-0.19, 0.27	0.733
Inh + Continued Met, Baseline HbA1c >9.5-12	109	10.4 (0.7)	7.5 (1.1)	-2.9 (1.2)	-0.37	-0.62, -0.12	0.004
Glibenclamide + Continued Met, Baseline HbA1c >9.5-12	103	10.6 (0.7)	8.0 (1.2)	-2.6 (1.2)			

a Least Squares Means based on the primary model with terms for baseline, treatment and center
Source: Applicant's Tables 5.2.1.2 and 5.2.1.3, Study 1002 report

Please see Table 6.2.4.2.1 for change from baseline in HbA1c for Study 109. In that study, inhaled insulin plus continued failed oral agent therapy was superior to continued failed oral agent therapy for change in HbA1c. As discussed in Section 6.2.4.2.1, inhaled insulin monotherapy was also superior to continued failed oral agent therapy; inhaled insulin plus failed oral agent therapy resulted in a greater mean decline in HbA1c than inhaled insulin monotherapy (-1.9% vs -1.4%).

6.4.4.3 Secondary Endpoints

6.4.4.3.1 Treatment to Goal

In Study 1001, for patients with baseline HbA1cs 8-9.5, a numerically higher percentage of patients in the inhaled insulin + continued SU group achieved HbA1cs of <8%; there was no difference between groups for the percentage of patients who achieved HbA1cs <7%.

Table 6.4.4.3.1.1 Percentage of Patients Achieving HbA1c <8% and <7%, Study 1001, ITT Population, Baseline HbA1c 8-9.5%

	N	BL # pts (%)	End-of Study # pts (%)	Odds Ratio (Inh Ins +Continued SU Grp vs Metformin + Continued SU Grp)	95% CI Limits for Odds Ratio
<8%					
Inh Ins + Continued SU	101	6 (5.9)	82 (81.2)	1.78	0.86, 3.69
Met + Continued SU	93	8 (8.6)	68 (73.1)		
<7%					

Table 6.4.4.3.1.1 Percentage of Patients Achieving HbA1c <8% and <7%, Study 1001, ITT Population, Baseline HbA1c 8-9.5%

	N	BL # pts (%)	End-of Study # pts (%)	Odds Ratio (Inh Ins +Continued SU Grp vs Metformin + Continued SU Grp)	95% CI Limits for Odds Ratio
Inh Ins + Continued SU	101	0	31 (30.7)	0.96	0.51, 1.79
Met + Continued SU	93	0	30 (32.3)		

Source: Applicant's Table 22, NDA Section 2.7.3.3.2.2.2; Tables 5.3.1.1.2, 5.3.1.1.3, and 5.3.2.1.2, Study 1001 report

In Study 1001, for patients with baseline HbA1cs >9.5-12%, a slightly larger percentage of patients in the inhaled insulin add-on group achieved HbA1cs <8% than did patients in the metformin add-on group. For patients with baseline HbA1cs >9.5-12%, few patients achieved HbA1c <7% in either group, but a larger percentage of patients in the inhaled insulin add-on group achieved this goal than did patients in the metformin add-on group.

Table 6.4.4.3.1.2 % of Patients Achieving HbA1c <8% and <7%, Study 1001, ITT Population, Baseline HbA1c >9.5-12%

	N	BL # pts (%)	End-of Study # pts (%)	Odds Ratio (Inh Ins +Continued SU Grp vs Metformin + Continued SU Grp)	95% CI Limits for Odds Ratio
<8%					
Inh Ins + Continued SU	113	0	55 (48.7)	1.11	0.64, 1.93
Met + Continued SU	103	0	46 (44.7)		
<7%					
Inh Ins + Continued SU	113	0	23 (20.4)	1.45	0.69, 3.01
Met + Continued SU	103	0	15 (14.6)		

Source: Applicant's Table 22, NDA Section 2.7.3.3.2.2.2; Tables 5.3.1.1.2, 5.3.1.1.3, and 5.3.2.1.2, Study 1001 report

In Study 1002, for patients with baseline HbA1cs 8-9.5%, addition of the comparator agent (glibenclamide) was slightly superior to addition of inhaled insulin to failed metformin therapy, for percentage of patients achieving HbA1cs <8% and <7%.

Table 6.4.4.3.1.3 % of Patients Achieving HbA1c <8% and <7%, Study 1002, ITT Population, Baseline HbA1c 8-9.5%

	N	BL # pts (%)	End-of Study # pts (%)	Odds Ratio (Inh Ins +Continued Met Grp vs Glibenclamide + Continued Met Grp)	95% CI Limits for Odds Ratio
<8%					
Inh Ins + Continued Met	125		101 (80.8)		
Glibenclamide + Continued Met	119		103 (86.6)	0.49	0.23, 1.06
<7%					
Inh Ins + Continued Met	125		50 (40.0)		
Glibenclamide + Continued Met	119		51 (42.9)	0.85	0.49, 1.46

Source: Applicant's Table 22, NDA Section 2.7.3.3.2.2.2; Tables 5.3.1.1.2, 5.3.1.1.3, and 5.3.2.1.2, Study 1002 report

In Study 1002, for patients on failed metformin therapy with baseline HbA1cs >9.5-12%, addition of inhaled insulin appeared superior to addition of glibenclamide for percentage of patients achieving HbA1cs of <8% and <7%.

Table 6.4.4.3.1.4 % of Patients Achieving HbA1c <8% and <7%, Study 1002, ITT Population, Baseline HbA1c >9.5-12%

	N	BL # pts (%)	End-of Study # pts (%)	Odds Ratio (Inh Ins +Continued Met Grp vs Glibenclamide + Continued Met Grp)	95% CI Limits for Odds Ratio
<8%					
Inh Ins + Continued Met	109	0	79 (72.5)	1.91	1.02, 3.55
Glibenclamide + Continued Met	103	0	58 (56.3)		
<7%					
Inh Ins + Continued Met	109	0	37 (33.9)	2.54	1.27, 5.08
Glibenclamide + Continued Met	103	0	18 (17.5)		

Source: Applicant's Table 22, NDA Section 2.7.3.3.2.2.2; Tables 5.3.1.1.2, 5.3.1.1.3, and 5.3.2.1.2, Study 1002 report

Please see Table 6.2.4.2.2.1 for treatment to goal data for Study 109. In that study, inhaled insulin plus continued failed oral agent treatment was superior to continued failed oral agent treatment alone for the percentage of patients attaining HbA1cs of <8% and <7%. A higher percentage of patients achieved these goals with inhaled insulin plus continued failed oral agent treatment than with inhaled insulin monotherapy which was in turn superior to continued failed oral agent therapy alone (<8% HbA1c= 86% vs 56% vs 19% respectively; HbA1c <7% = 32% vs 17% vs 1% respectively).

6.4.4.3.2 Fasting and Postprandial Plasma Glucose

For Study both Studies 1001 and 1002, the change in fasting plasma glucose was similar between treatment groups for both HbA1c strata. For both Studies 1001 and 1002, the change in PPG

was similar between treatment groups for patients with baseline HbA1cs between 8 and 9.5%. For both Studies 1001 and 1002, addition of inhaled insulin to either failed SU or failed metformin therapy resulted in a greater favorable change in PPG than did addition of comparator.

Table 6.4.4.3.2.1 Mean Fasting Plasma Glucose and Mean Postprandial Glucose Excursion, Study 1001, ITT Population, Baseline HbA1c 8-9.5

		n	BL (SD)	End-of-study Change (SD)	Difference between Inh Ins + Continued SU Grp and Metformin + Continued SU Grp	95% CI Limits for Difference between Grps
FPG						
	Inh Ins + Continued SU	97	197 (45)	-33 (51)	4.27	-7.67, 16.20
	Metformin + Continued SU	90	198 (49)	- 38 (52)		
Two-hour Postprandial Glucose Change (from Preprandial Value)						
	Inh Ins + Continued SU	70	219 (39)	-57 (39)	-5.62	-15.96, 4.71
	Metformin + Continued SU	76	211 (38)	-46 (42)		

Source: Applicant's Tables 5.5.3.2, 5.5.3.3, 5.6.2, 5.6.3, Studies 1001 and 1002 reports

Table 6.4.4.3.2.2 Mean Fasting Plasma Glucose and Mean Postprandial Glucose Excursion, Study 1001, ITT Population, Baseline HbA1c >9.5-12

		n	BL (SD)	End-of-study Change (SD)	Difference between Inh Ins + Continued SU Grp and Metformin + Continued SU Grp	95% CI Limits for Difference between Grps
FPG						
	Inh Ins + Continued SU	107	241 (54)	-63 (55)	0.51	-10.75, 11.78
	Metformin + Continued SU	102	237 (53)	-60 (56)		
Two-hour Postprandial Glucose Change (from Preprandial Value)						
	Inh Ins + Continued SU	83	255 (48)	-91 (52)	-17.17	-27.35, -6.98
	Metformin + Continued SU	67	253 (48)	-73 (48)		

Source: Applicant's Tables 5.5.3.2, 5.5.3.3, 5.6.2, 5.6.3, Studies 1001 and 1002 reports

Table 6.4.4.3.2.3 Mean Fasting Plasma Glucose and Mean Postprandial Glucose Excursion, Study 1002, ITT Population, Baseline HbA1c 8-9.5

		n	BL (SD)	End-of-study Change (SD)	Difference between Inh Ins + Continued Met Grp and Glibenclamide + Continued Met Grp	95% CI Limits for Difference between Grps
FPG						
	Inh Ins + Continued Met	118	187 (46)	-32 (49)	3.82	-6.90, 14.54
	Glibenclamide + Continued Met	110	196 (42)	-43 (46)		
Two-hour Postprandial						

Table 6.4.4.3.2.3 Mean Fasting Plasma Glucose and Mean Postprandial Glucose Excursion, Study 1002, ITT Population, Baseline HbA1c 8-9.5

		n	BL (SD)	End-of-study Change (SD)	Difference between Inh Ins + Continued Met Grp and Glibenclamide + Continued Met Grp	95% CI Limits for Difference between Grps
Glucose Change (from Preprandial Value)						
	Inh Ins + Continued Met	101	200 (43)	-46 (46)	-3.65	-13.73, 6.44
	Glibenclamide + Continued Met	86	206 (36)	-48 (44)		
Source: Applicant's Tables 5.5.3.2, 5.5.3.3, 5.6.2, 5.6.3, Studies 1001 and 1002 reports						

Table 6.4.4.3.2.4 Mean Fasting Plasma Glucose and Mean Postprandial Glucose Excursion, Study 1002, ITT Population, Baseline HbA1c >9.5-12

		n	BL (SD)	End-of-study Change (SD)	Difference between Inh Ins + Continued Met Grp and Glibenclamide + Continued Met Grp	95% CI Limits for Difference between Grps
FPG						
	Inh Ins + Continued Met	93	223 (61)	-55 (58)	-1.85	-14.00, 10.30
	Glibenclamide + Continued Met	87	243 (58)	-65 (60)		
Two-hour Postprandial Glucose Change (from Preprandial Value)						
	Inh Ins + Continued Met	86	236 (50)	-78 (51)	-18.51	-29.04, -7.97
	Glibenclamide + Continued Met	84	250 (49)	-70 (50)		
Source: Applicant's Tables 5.5.3.2, 5.5.3.3, 5.6.2, 5.6.3, Studies 1001 and 1002 reports						

Please see Table 6.2.4.2.2.2 for fasting and postprandial glucose data for Study 109. In that study, inhaled insulin plus continued failed oral agent therapy was superior to continued failed oral agent therapy alone for reduction of fasting plasma glucose and postprandial glucose excursion. Reductions in these parameters were greater with inhaled insulin plus continued failed oral agent therapy than with inhaled insulin monotherapy; inhaled insulin monotherapy was also superior to continued failed oral agent therapy.

6.4.5 Clinical Microbiology

Not applicable.

6.4.6 Efficacy Conclusions

For Study 1001, for the primary efficacy endpoint of change from baseline in HbA1c, the 6-month data did not support superiority of the addition of inhaled insulin over the addition of sulfonylurea to failed metformin therapy. For Study 1002, for the primary efficacy endpoint of

change from baseline in HbA1c, the 6-month data did not support superiority of the addition of inhaled insulin over the addition of metformin to failed sulfonylurea therapy. However, for both studies, the addition of inhaled insulin appeared noninferior to the addition of the comparator oral agent. In Study 109, the addition of inhaled insulin to continued failed combined oral agent therapy appeared superior to continued failed combined oral agent therapy alone for change from baseline in HbA1c at 3 months.

For both Studies 1001 and 1002, the addition of inhaled insulin resulted in a greater percentage of patients achieving HbA1cs <8% than did addition of the comparator agent. Patients with higher HbA1cs at baseline (>9.5-12%) were more likely to achieve a HbA1c <7% with the addition of inhaled insulin than with the addition of the comparator, although the percentage of patients in either treatment group who achieved a HbA1c <7% was small. In Study 109, the addition of inhaled insulin to continued failed combined oral agent therapy appeared superior to continued failed combined oral agent therapy alone for achievement of HbA1cs <8% and <7%.

Overall, the addition of inhaled insulin to a failed oral agent appears at least noninferior to the addition of a second oral agent for the control of Type 2 diabetes. Addition of inhaled insulin to failed combined oral agent therapy appears superior to continued failed oral agent therapy alone. The combination of inhaled insulin and failed combined oral agent therapy resulted in greater favorable changes in measures of glucose control in Type 2 diabetes than did inhaled insulin monotherapy, which in turn was also superior to continued failed combined oral agent therapy alone.

6.5 Potential Off-label Use: Treatment of Hyperglycemia in Pediatric Patients with Type 1 Diabetes, Inhaled Insulin in Combination with Longer-acting Insulins

6.5.1 Methods

The applicant is not seeking an indication for pediatric use for Exubera®. However, the clinical reviewer anticipates significant interest in the use of the product for children, with the potential for off-label use. Studies 106 and 107 included adolescents ages 12-17 years, and Study 1009 included children ages 6-11 years. No children ages 5 and under were studied.

6.5.2 General Discussion of Endpoints

For all three studies, the primary endpoint was change from baseline in HbA1c. HbA1c is likely a valid surrogate for the risk for development of microvascular complications in Type 1 diabetes, as discussed in Section 6.1.2.

6.5.3 Study Design

Please see Section 6.1.3 for a description of the design of Studies 106 and 107. Study 1009 was a 3-month, open-label, block-allocated, parallel group efficacy and safety study conducted in Type 1 diabetic children ages 6-11 years. A total of 120 children were treated with either an

inhaled insulin regimen (TID premeal inhaled insulin + hs or BID UL or NPH) or a SQ regimen (BID lispro or regular + q day or BID UL or NPH). Secondary endpoints and special safety evaluations were similar to those in Studies 106 and 107.

6.5.4 Efficacy Findings

6.5.4.1 Primary Endpoint

There was little difference between treatment groups for change from baseline in HbA1c in Studies 106, 107 and 1009. Neither treatment group attained "tight" control of mean HbA1c in any of these studies. Inhaled insulin patients had little change from baseline in HbA1c.

Table 6.5.4.1 Change from Baseline in HbA1c, Patients < Age 18 years, ITT Populations, Studies 106, 107 and 1009[1]

Study	Group	N	BL (SD)	Change from Baseline (SD)	LSM Difference between Treatment Groups	95% CI Limits for Difference between Groups	p-Value
106	Inh Ins	33	8.6 (1.0)	0 (1.2)	+ 0.3	-0.09, 0.7	NS
	SQ	29	8.5 (0.8)	-0.3 (0.7)			
107	Inh Ins	59	8.3 (0.9)	-0.2 (0.8)	-0.2	-0.5, 0.1	NS
	SQ	59	8.3 (0.9)	0 (1.1)			
1009	Inh Ins	60	8.1 (0.7)	-0.3 (0.1)	-0.2	-0.5, 0.03	NS
	SQ	59	8.1 (0.8)	0 (0.1)			

1 Studies 106 and 107 analyses at 6 months, patients ages 11-17 yrs; Study 1009 analysis at 3 months, patients ages 6-11 years
Source: Analyses for Studies 106 and 107 by Dr. Mele, Biostatistics; Table 5.2.1, Study 1009 report

6.5.4.2 Secondary Endpoints

6.5.4.2.1 Treatment to Goal

Analyses of secondary endpoints were not provided for adolescents in Studies 106 and 107.

In Study 1009, a slightly larger percentage of children ages 6-11 achieved HbA1cs <8% and <7% in the inhaled insulin group than did children in the SQ group.

Table 6.5.4.2.1 Percentage of Children Achieving HbA1c <8% and <7%, Study 1009, Per Protocol Population

	N	BL # pts (%)	12 Weeks # pts (%)	Odds Ratio (Inh Ins Grp vs SQ Grp)	95% CI Limits for Odds Ratio
<8%					
Inh Ins	60	25 (41.7)	33 (55.0)	1.44	0.57, 3.63
SQ	59	23 (39.0)	28 (47.5)		
<7%					

Table 6.5.4.2.1 Percentage of Children Achieving HbA1c <8% and <7%, Study 1009, Per Protocol Population

	N	BL # pts (%)	12 Weeks # pts (%)	Odds Ratio (Inh Ins Grp vs SQ Grp)	95% CI Limits for Odds Ratio
Inh Ins	60	3 (5.0)	11 (18.3)	1.81	0.53, 6.12
SQ	59	5 (8.5)	10 (16.9)		

Source: Applicant's Tables 5.3.1.2 and 5.3.2.2, Study 1009 report; baseline percentages from Section 11, Item 11, Table 2.2. Study 1009 report

6.5.4.2.2 Fasting and Postprandial Plasma Glucose

In Study 1009, mean fasting plasma glucoses remained undesirably high in both treatment groups, with no significant difference between groups. There was no significant difference between groups for change in postprandial glucose excursion, with small declines in both treatment groups.

Table 6.5.4.2.2 Mean Fasting Plasma Glucose and Mean 2-hr Postprandial Glucose Excursion on HBGM, Study 1009, Per Protocol Population

		n	BL (SD)	Wk 12 Change (SD)	Difference between Inh Ins Grp and SQ Grp	95% CI Limits for Difference between Grps
FPG						
	Inh Ins	58	200 (61)	3 (11)	-1.85	-33.25, 29.54
	SQ	58	193 (86)	5 (11)		
Two-hour Postprandial Glucose Change (from Preprandial Value)						
	Inh Ins	43	27.3 (51.3)	-18.9 (11.3)	-4.15	-31.13, 22.82
	SQ	46	22.9 (56.9)	-14.7 (10.1)		

Source: Applicant's Tables 5.6.1 and 5.5.4, Study 1009 report

6.5.5 Clinical Microbiology

Not applicable.

6.5.6 Efficacy Conclusions

Although children in the inhaled insulin and SQ treatment groups had similar values for change from baseline in HbA1c for Studies 106, 107 and 1009, the clinical reviewer is unable to conclude that inhaled insulin was noninferior to subcutaneous insulin, because there was little change from baseline in either group, and mean HbA1c at end of study did not fall into the desirable range for control of Type 1 diabetes. In Study 1009, a slightly higher percentage of children in the inhaled insulin group achieved HbA1cs <7% and <8% than did children in the subcutaneous group. There was no significant difference between groups for changes in fasting plasma glucose and postprandial glucose excursion.

Studies performed in children and adolescents to date do not show that the desirable level of glucose control (i.e. that associated with decreased risk for later diabetic complications) can be achieved with inhaled insulin. Should Exubera® be approved for use in adults, further study in children is warranted.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

A total of 22 deaths occurred among 3,603 subjects (0.6%) exposed to inhaled insulin in the clinical development program, as of the safety cut-off date of 1 Sep 04. Of these, 21 patients were participants in the clinical development program and one was a neonate born of a mother exposed to inhaled insulin. Ten deaths, including that of the neonate, occurred during controlled Phase 2/3 trials, which included 1,975 adult patients (0.5%). Twelve deaths occurred during extension studies, which included 1,449 patients (0.8%).

Five patients who received comparator drugs died, out of 1,938 comparator patients (0.3%).

The following tables summarize deaths occurring in the inhaled insulin and comparator groups.

Table 7.1.1.1.1
Deaths Listing[1]
Treatment = Exubera®
Cutoff Date: 1 Sep 04

Trial	Center	Patient	Age (yrs)	Gender	Total Daily Dose[2] (mg)	Time (days)[3]	Source[4]	Description
102E	5007	0106	57	M	23	1073	N	Ischemic heart disease
102E	5011	0077	35	F	5	1460	N	Automobile accident (MVA)
103E	5006	0048	62	M	27	1016 (3)	N	Acute myocardial infarction (AMI)
104E	5016	0005	65	M	24	950 (3)	N	AMI
104E	5016	0007	63	M	13	1772	N	Cardiopulmonary arrest
108	5010	8003	75	M	9	121 (1)	N	Gastrointestinal (GI) bleed, esophageal cancer
108	5048	8119	48	M	24	65 (14)	N	Esophageal bleed
111	5044	8013	73	M	12	669 (6)	N	Multiorgan failure
111	5046	8336	76	M	22	907 (10)	N	AMI
111	5048	0412	64	M	6	592	N	Cerebral hemorrhage
111	5048	0414	73	M	6	240	N	AMI, possible fall from ladder
111	5049	6770	54	F	14	328 (8)	N	MI
1001	0004	0025	63	M	19	307 (23)	N	Ventricular tachycardia (V tach)
1001	0134	1373	66	M	4	13 (11)	N	Acute MI, ventricular fibrillation
1022	1016	0891	51	M	10	229	N	MI
1022	1039	NS01[5]	0 (2 days)	M	7	28 (194)	N	Congestive heart failure
1022	5152	3622	48	F	13	27 (25)	N	MI
1022	5154	3682	58	M	15	353	N	Found dead at home
1027	1016	0648	49	M	3	89 (1)	N	MI after hypoglycemic episode
1029	1026	0659	61	M	22	307 (6)	N	Metastatic colon cancer
1036	5005	1006	70	M	32	97	N	MI
1036	5011	1004	48	F	18	2367	N	MI

1 Includes all deaths that occurred during drug exposure, or within 30 days following discontinuation from drug, or later but resulting from adverse events that had onset during drug exposure or had onset within 30 days following drug exposure
2 Dose at time of death. If died after discontinuation, last dose prior to discontinuation
3 Days on drug at time of death. If death occurred after discontinuation, includes number of days on drug before discontinuation followed, in parentheses, by number of days off drug prior to death
4 N = NDA
5 Newborn infant of study subject who conceived while in inhaled insulin. Mother received inhaled insulin for appr 3-4 wks postconception. Last dose = 7 mg. Drug discontinued upon discovery of pregnancy; infant died 6 months later, 2 days postpartum

Table 7.1.1.1.2
Deaths Listing[1]
Treatment = Comparator
Cutoff Date: 1 Sep 04

Trial	Center	Patient	Age (years)	Gender	Comparator	Dose[2] (mg)	Time (Days)[3]	Source[4]	Description
1002	0005	5030	64	M	Glibenclamide	2.5	89	N	Automobile accident
					Metformin	2000	89		
1002	0047	6086	59	M	Glibenclamide	10	83	N	Acute myocardial infarction (AMI)
					Metformin	2000	110		
1002	0096	5203	62	M	Glibenclamide	5	64 (3)	N	MI
					Metformin	2500	64 (3)		
1030	1032	3085	64	M	Isophane insulin	49	84 (9)	N	MI
					Regular insulin	19	84 (9)		
					Metformin	1000	93		
					Glipizide	10	93		
1030	1055	5665	73	M	Isophane insulin	32	135?	N	Sudden death at home
					Regular insulin	10	135		

1 Includes all deaths that occurred during drug exposure, or within 30 days following discontinuation from drug, or later but resulting from adverse events that had onset during drug exposure or had onset within 30 days following drug exposure
2 Dose at time of death. If died after discontinuation, last dose prior to discontinuation
3 Days on drug at time of death. If death occurred after discontinuation, includes number of days on drug before discontinuation followed, in parentheses, by number of days off drug prior to death
4 N = NDA

The following table details mortality by treatment group.

Table 7.1.1.2
Mortality by Treatment Group
Pool of Phase 2 and Phase 3 Studies with Inhaled Insulin
Cutoff Date 1 Sep 04

Treatment Group	Total Number of Patients	Total Number of Deaths	Crude Mortality	Patient Exposure Years (PEY)	Total Deaths with Person-Time	Mortality per PEY
Inhaled Insulin	2787	22	0.8 %	3938.2	22	0.6
SQ Insulin	1365	2	0.1 %	910.0	2	0.2
Oral Agents	648	3	0.5 %	537.7	3	0.5
Source: Applicant's Tables 3, 5 and 6, ISS pages 18-20						

When taking into account the longer duration of exposure for inhaled insulin groups, there is little difference in mortality rates between inhaled insulin and comparator treatments.

Death Narratives

A brief summary of each death narrative for inhaled insulin group patients follows. Patients are identified by their study number, then their center number, then their patient ID number.

102E-5007-0106: 57 year old (yo) man with Type 1 DM, complicated by (c/b) retinopathy and neuropathy, who received inhaled insulin 5.1-26.8 mg/day for 1073 days. Also received extended zinc suspension insulin. On Study Day 1073, while on a boating outing, developed chest heaviness, vomited twice, and collapsed. CPR performed, but patient (pt) pronounced dead at scene by paramedics. Autopsy listed cause of death as ischemic heart disease.

102E-5011-0077: 35 yo woman with Type 1 DM who received inhaled insulin, 3-7.6 mg/day, for 1460 days. Also received extended zinc suspension insulin. On Study Day 1460, had a motor vehicle accident (MVA) while driving home after dinner with friends. Friends state she had no alcohol, but had blood alcohol level of 201 mg/dL. Blood glucose (BG) at scene 120 mg/dL. No skid marks at scene. Pronounced dead at scene; autopsy revealed multiple internal and external injuries.

103E-5006-0048: 62 yo man with Type 2 DM c/b hypertension (htn), neuropathy. Received inhaled insulin 17.7-32.1 mg/day for 1016 days. Also received extended zinc suspension insulin. Acute MI on Study Day 1016; died on Study Day 1019, 3 days after last dose of inhaled insulin.

104E-5016-0005: 65 yo man with Type 2 DM c/b retinopathy and htn. Received inhaled insulin 17.4-23.9 mg for 950 days. Also received glibenclamide. At 6 mo of study, had a 25% decline in forced expiratory volume in one second (FEV1) and a 21% decline in forced vital capacity (FVC). Had numerous hypoglycemic episodes, which the applicant describes as mild, and two episodes of moderate hypoglycemia. On Study Day 953, had acute MI while at racetrack; pronounced dead on arrival (DOA) at emergency room (ER).

104E-5016-0007: 63 yo man with Type 2 DM c/b hyperlipoproteinemia (HLP) and cardiomegaly. Received inhaled insulin, 8.1-13.3 mg/day, for 1858 days. Also received

glibenclamide. On Study Day 1858, collapsed at church after complaining of chest pain. In ventricular fibrillation (V fib) when paramedics arrived. Prolonged resuscitation attempt in ER failed. BG in ER 132 mg/dL. FEV1 had declined 16% from baseline by Study Day 817, and 19% by Study Day 1822.

108-5010-8003: 75 yo man with Type 2 DM, c/b nephropathy and neuropathy, received inhaled insulin at doses ranging from 11.3-25.2 mg, for 116 days. Also received zinc suspension insulin. On Study Day 116, developed melena, was hospitalized, and found to have esophageal cancer. Inhaled insulin stopped on admission. Died on Study Day 122 of gastrointestinal (GI) bleeding and progression of cancer.

108-5048-8119: 48 yo man with Type 2 DM, c/b neuropathy, received 17.2-19.5 mg inhaled insulin for 65 days. Also received extended zinc suspension insulin. On Study Day 65, hematemesis and hospitalization. Esophageal bleed diagnosed; underwent band ligation. Condition deteriorated and patient required mechanical ventilation. Died on Study Day 78 of esophageal bleed.

111-5044-8013: 73 yo man with Type 2 DM. Received inhaled insulin, 13-26.9 mg/day, for 669 days. Also received insulin glargine and extended zinc suspension insulin. On Study Day 637, investigator noted cardiac arrhythmia on subject's electrocardiogram (ECG) and referred pt to ER emergently (stat). Pt refused to go, stating he had to catch a plane to Arizona. On Study Day 670, presented to ER with acute renal failure, congestive heart failure, atrial fibrillation, elevated liver function tests (LFTs), and hyperammonemia. Inhaled insulin was discontinued. Developed progressive liver failure and was found to be positive for Hepatitis B and C. Developed esophageal bleeding and anuria. On Study Day 675, family chose to discontinue care due to multiorgan failure.

111-5046-8336: 76 yo man with Type 2 DM c/b retinopathy, neuropathy, htn, coronary heart disease (CHD), atherosclerotic peripheral vascular disease (ASPVD). Received inhaled insulin, 10.8-24.5 mg/day, for 907 days. Died in his sleep at home on Study Day 917. No autopsy done; death certificate listed cause of death as cardiac arrest, acute myocardial infarction and coronary artery disease. Pt had had decline in diffusion capacity for carbon monoxide (DLco).

111-5048-0412: 64 yo man with Type 2 DM c/b htn. Also had history of (hx) recurrent deep venous thrombosis (DVT) and was on warfarin. Received inhaled insulin, 7.1-12.2 mg/day for 592 days. Also received metformin. On Study Day 589, was punched in the face during an altercation. Later that day, complained of headache and went to hospital. Died on Study Day 592 of cerebral hemorrhage (autopsy done).

111-5048-0414: 73 yo man with Type 2 DM c/b HLP, htn, CHD, hx coronary artery bypass grafting (CABG). Received inhaled insulin, 1-2 mg/day, for 240 days. Also received glipizide and metformin. On Study Day 240, had been painting on a ladder at a neighbor's house. Was found dead on the ground by his wife. Autopsy revealed "massive" MI.

111-5049-6770: 54 yo woman with Type 1 DM. Received inhaled insulin, 8.2-14.4 mg/day, for 328 days. Also received extended zinc suspension insulin. On Study Day 329, found unresponsive and diagnosed with MI. Placed on mechanical ventilatory support; family decided to discontinue ventilator on Study Day 335 and pt died on Study Day 336.

1001-0004-0025: 63 yo man with Type 2 DM, c/b angina pectoris, who received inhaled insulin 6.5-22.4 mg/day for 306 days. Also received glibenclamide. On Study Day 307, admitted to hospital with chest pain. Inhaled insulin discontinued. Developed v fib and was resuscitated. Found to have extensive anterior wall MI. Developed pneumonia, sepsis, congestive heart failure (CHF), multiple episodes ventricular tachycardia (V tach). Died on Study Day 330, 24 days after last dose of inhaled insulin, of V tach.

1001-0134-1373: 66 yo man with Type 2 DM c/b htn and ischemic heart disease, who received inhaled insulin 4 mg/day for 13 days. On Study Day 13, experienced chest pain at rest. Admitted to hospital with acute MI. Inhaled insulin stopped. Underwent CABG on Study Day 22; deteriorated and died of ventricular fibrillation on Study Day 24, 11 days after last dose of inhaled insulin.

1022-1016-0891: 51 yo man with Type 1 DM, c/b retinopathy, received 10-11 mg inhaled insulin per day for 229 days. Also received insulin glargine (glargine). Died on study day 229 due to MI- no autopsy.

1022-1039-NS01: 2 day old neonate born of a study subject. Born preterm with macrosomia and cardiomegaly, and died of congestive heart failure and cardiogenic shock. Mother was a 22 yo woman with Type 1 DM who received inhaled insulin 7 mg/day for 110 days. Also received isophane insulin. Was taking oral contraceptive pills (OCP). On Study Day 72, had last menstrual period (LMP). Mother was unaware of pregnancy until Study Day 111, when she had a positive pregnancy test. Inhaled insulin stopped, and switched to isophane and regular insulins, and insulin lispro. On Study Day 261, 150 days after last dose of inhaled insulin, fetal ultrasound revealed macrosomia and polyhydramnios. On Study Day 292, 181 days after last dose of inhaled insulin, mother experienced preterm labor at 31 wks EGA. Treated with tocolytics. On Study Day 295, mother developed diabetic ketoacidosis (DKA). On Study Day 297, Caesarian section. Neonate macrosomic and had cardiomegaly. Neonate developed congestive heart failure and cardiogenic shock and died on Day 2 of life.

1022-5152-3622: 48 yo woman with 40 year history Type 1 DM c/b retinopathy, nephropathy, HLP and htn. Received average dose of inhaled insulin of 13 mg/day for 27 days; was withdrawn from study due to noncompliance. Also received extended zinc suspension insulin. Died of MI 25 days after last dose of inhaled insulin.

1022-5154-3682: 58 yo man with Type 1 DM c/b retinopathy, HLP and htn. Received inhaled insulin in doses ranging from 10-22.7 mg/day for 353 days. Also received isophane insulin. Patient was found dead at home; reported to have been dead for 24 hours.

1027-1016-0648: 49 yo man with Type 1 DM, c/b prior MI, received inhaled insulin, 4.4-6.0 mg for 89 days. Also received glargine. After three months of inhaled insulin, complained of headaches, which had been a rare occurrence for him in the past. Had acupuncture on study day 89. That evening, had a large meal, followed by a blood sugar of 350 mg/dL. Gave himself aspart insulin (dose unknown). Shortly before midnight, asked his wife for juice for a possible low blood sugar. Patient then had a seizure with incontinence of urine, and became unresponsive. EMS performed CPR en route to ER; patient died a few hours later. Autopsy revealed cause of death as MI. Old MI also noted on autopsy.

1029-1026-0659: 61 yo man with Type 2 DM c/b retinopathy, macular edema and history of foot ulcer. Received inhaled insulin, 30.4-41.1 mg/day for 307 days. Also received insulin glargine. On Study Day 226 was diagnosed with widely metastatic colon cancer. Died on Study Day 313, 6 days after last dose of inhaled insulin.

1036-5005-1006: 70 yo man with Type 2 DM c/b htn, CHD. Also had history of (hx) aortic valve replacement (AoVR). Received inhaled insulin, 9 mg/day, for 97 days. Also received isophane insulin and glibenclamide. On Study Day 97, collapsed at home after playing golf and swimming. Wife reported that patient had "massive" myocardial infarction. No autopsy.

1036-5011-1004: 48 yo woman with Type 2 DM c/b htn, HLP and retinopathy. Received inhaled insulin, for 2367 days (over 3 studies). Also received insulin glargine, rosiglitazone, metformin and glibenclamide. On inhaled insulin administration day 2367, began choking and coughing while riding as a passenger in a car. Was given epinephrine and atropine *en route* to hospital; arrived in full arrest. Resuscitation unsuccessful. Cause of death listed as MI; no autopsy performed.

Discussion of Deaths

Of the adult patients who died during the clinical development program, 15/21 appear to have died of cardiac causes. Most diabetics die of cardiovascular disease, and the percentage of deaths which were due to cardiovascular disease during the study of this product is consistent with the usual incidence of cardiovascular death among diabetics.

A total of 7/21 of these deaths occurred in Type 1 diabetics who were taking inhaled insulin. In a metaanalysis of randomized controlled trials (including the DCCT) of intensive management of Type 1 diabetes, 15/1028 (1.5%) of patients in intensive insulin treatment groups died (Egger 1997). In this development program, 7/1209 (0.6%) of Type 1 patients who were exposed to inhaled insulin in the entire development program died, and 4/851 (0.5%) of those in controlled Phase 2 and Phase 3 trials died. In the Eggers metaanalysis, 5/1028 (0.5%) of patients died of sudden death or macrovascular disease, compared to 6/1209 (0.5%) of Type 1 patients in this development program, and 4/851 (0.5%) in controlled Phase 2 and Phase 3 trials. The rate of death among Type 1 inhaled insulin patients does not exceed that found in the intensive treatment groups of large randomized trials in Type 1 diabetics. Mean age at death for Type 1 diabetics in this development program was 50.2 years. An extensive literature and insurance actuarial data search by the clinical reviewer did not reveal data regarding expected mean age at

death for Type 1 diabetics. In developed countries, mortality for Type 1 diabetes is approximately 30% by age 55 years (Muller 1998). Mean age of Type 1 diabetics at entry into study was 38 years for both inhaled and SQ groups. Patients who were older at entry were at greater risk for cardiovascular mortality. Patients with recent cardiovascular events were excluded from study, but those with established coronary artery disease without recent events were not excluded.

Mean age at death for Type 2 diabetics treated with inhaled insulin was 64.8 years; mean age at study entry was 57.2 years. Patients who were older at entry were more likely to have atherosclerotic disease. Patients with recent cardiovascular events were excluded from study, but those with established coronary artery disease without recent events were not excluded.

In trials of intensive management of diabetes, severe hypoglycemic events with resultant injury or death have been a concern. The clinical reviewer searched for hypoglycemic event histories for those patients who died of injury, myocardial infarction or apparent sudden cardiac death (n = 14).

Table 7.1.1.3: Hypoglycemic Event and HbA1c Data for Patients who Died of MI or other Sudden Causes

Patient ID	Type DM	Baseline HbA1C	Last HbA1C	Total Number Severe Hypoglycemic Episodes[1]	Number Severe Hypoglycemic Episodes Recorded in Month Before Death
102E-5011-0077	1	no dataset[2] (8.4)	8.2	1	0
103E-5006-0048	2	no dataset (7.9)	9.6	0	0
104E-5016-0005	2	no dataset (10.6)	7.1	0	0
111-5046-8336	2	7.7	7.5	0	0
111-5048-0414	2	8.4	7.7	0	0
111-5049-6770	1	8.2	7.3	0	0
1001-0004-0025	2	9.1	8.3	0	0
1001-0134-1373	2	10.1	10.1	0	0
1022-1016-0891	1	no dataset (8.0)	7.6	0	0
1022-5152-3622	1	no dataset (8.6)	7.8	0	0
1022-5154-3682	1	no dataset (6.1)	6.8	0	0
1027-1016-0648	1	no dataset (7.6)	6.5	0	0
1036-5005-1006	2	no dataset (9.0)	7.7	1	0
1036-5011-1004	2	no dataset (8.4)	7.5	0	0

1 Severe = requiring the assistance of another person and/or BG ≤ 36 mg/dL
2 For patients for whom there was no dataset, the clinical reviewer requested data from the sponsor. This is contained in their submission of 10 Jun 05, Table 2

Those patients who died of acute causes do not appear to have an unusually high incidence of severe hypoglycemic events (those requiring the assistance of another person, or events with a blood sugar <36 mg/dL). However, four of these patients had histories of a large number of nonserious hypoglycemic events. Patient 102E-5011-0077, a 35 year old woman who died in a motor vehicle accident, had a history of 147 nonserious hypoglycemic events over her 1463 days of inhaled insulin treatment. However, her blood sugar at the accident scene was recorded as 120 mg/dL. Patient 104E-5016-0005, a 65 year old man who died of an acute myocardial infarction, had 37 episodes of nonserious hypoglycemia over 1037 days of inhaled insulin treatment. Patient 1022-5154-3682, a 58 year old man who was found dead at home, had 116 nonserious hypoglycemic episodes over 352 days of inhaled insulin treatment. Patient 1027-1016-0648, a 49 year old man who died of a myocardial infarction, asked for juice for what he felt was a low blood sugar; he then suffered a seizure and died a few hours later of an MI. This patient had had 19 nonserious episodes of hypoglycemia over 89 days of inhaled insulin treatment.

Overall, the deaths which occurred in inhaled insulin group patients do not seem to have a stronger association with hypoglycemia than expected in diabetics treated with subcutaneous insulin. It is an unfortunate fact that tight glycemic control comes with a price of periodic episodes of severe hypoglycemia, which under certain circumstances can lead to death from accidents or acute cardiovascular events. As discussed in Sections 5.1 and 5.2, Exubera® has problems with dose proportionality and dose equivalence which are unique to this form of inhaled insulin administration, which do not occur with subcutaneous insulin, and which may increase the risk for hypoglycemia.

Three of the patients who died, all Type 2 diabetics, had significant declines in one or more pulmonary function tests prior to death. A significant decline was defined as a decrease of >15% in FEV1, FVC or TLC; or >20% in DLco. These 3 patients represent 21.4% (3/14) of the Type 2 diabetic patients who died. The incidence of significant declines in one or more pulmonary function tests in the controlled Phase 2/3 population of Type 2 diabetics was 13.1% (167/1277). All three of these patients died of apparent cardiac causes. The number of deaths is too small to permit meaningful statistical comparisons between the incidences of abnormal pulmonary function tests among Type 2 diabetics who died and the overall Type 2 diabetic population. However, a significant decline in pulmonary function could have more serious consequences for a patient with underlying cardiac disease and an already decreased ability to deliver oxygen to the myocardium, than for a patient without underlying cardiac disease.

In summary, the percentage of deaths among inhaled insulin patients in the development program does not exceed that seen in comparator patients, and does not exceed that seen in major diabetes trials. The causes of deaths are in general what one expects for diabetics, i.e. predominantly cardiovascular causes. The age at death of inhaled insulin patients does not appear to be lower than expected among diabetics in general, but hard statistics do not exist for expected age at death for diabetics in the general population. Patients who died of acute causes do not appear to have had a significant number of severe hypoglycemic events over the course of their participation in the trials, although some had a large number of nonserious hypoglycemic events, and one patient died shortly after what appears to have been a hypoglycemic episode. No

clear difference was demonstrated between inhaled insulin and comparator patients for incidence or cause of death.

7.1.2 Other Serious Adverse Events

For purposes of this review, a serious adverse event is defined as an event that results in any one of the following outcomes:

- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- persistent or significant disability or incapacity
- a congenital anomaly or defect

The applicant's definition of serious adverse events was essentially the same. Investigators for the clinical trials included in the application may also have considered other events serious, even if they did not strictly meet the above outcome criteria; these events are also included in the serious adverse event review.

Adverse event terms were coded using MedDRA and COSTART terminology.

7.1.2.1 Serious Adverse Events by Type of Event

7.1.2.1.1 Serious Adverse Events in Type 1 Adult Patients

In controlled Phase 2 and Phase 3 studies in Type 1 patients, serious adverse events occurred at a slightly higher frequency in SQ group patients than in inhaled insulin group patients, when comparing subject-months of exposure. The frequency of serious adverse events by exposure in inhaled insulin group patients was comparable in the controlled and overall Phase 2/3 populations.

Table 7.1.2.1.1.1 All-causality Serious Adverse Event Frequency in Type 1 Patients

	n	Subject-Months of Exposure (SME)	All-causality SAE Cases	All-Causality SAE Cases per 1,000 SME
Controlled Phase 2/3 Studies, Inh Ins	698	5,894	52	8.8
Controlled Phase 2/3 Studies, SQ	705	6,052	73	12.1
All Phase 2/3 Studies, Inh Ins	1,209	16,571	129	7.8

Source: Applicant's Tables 1.1.1, 2.1.1.1, 2.1.1.2, 2.2.1.1, 2.2.1.2, 6.1.1.2, 6.1.2.2, 6.2.1.2, 6.2.2.2, ISS Appendix

The most common serious adverse events among Type 1 patients were hypoglycemia and loss of consciousness. In the controlled Phase 2/3 population, these occurred with slightly greater frequency in SQ patients than in inhaled insulin patients. The following table lists the types of SAEs that occurred in the controlled Phase 2/3 population.

Table 7.1.2.1.1.2 Serious Adverse Events Occurring in Adult Type 1 Patients, Controlled Phase 2/3 Studies

MedDRA System Organ Class	MedDRA Preferred Event Term	Inh Ins total n = 698 # events (# events per 100 patients)	SQ total n = 705 # events (# events per 100 patients)
Cardiac Disorders		5 (0.7)	6 (0.9)
	Angina pectoris	1 (0.1)	0
	Angina unstable	0	1 (0.1)
	Coronary artery disease	0	2 (0.3)
	Myocardial infarction	3 (0.4)	2 (0.3)
	Sinus arrhythmia	0	1 (0.1)
	Sinus tachycardia	0	1 (0.1)
	Supraventricular tachycardia	1 (0.1)	0
Eye disorders		2 (0.3)	1 (0.1)
	Eye hemorrhage	1 (0.1)	0
	Macular degeneration	1 (0.1)	0
	Retinal detachment	0	1 (0.1)
Gastrointestinal disorders		2 (0.3)	4 (0.6)
	Abdominal hernia	1 (0.1)	0
	Colonic polyp	0	1 (0.1)
	Gastritis	1 (0.1)	0
	Gastrointestinal disorder	0	1 (0.1)
	Peptic ulcer	0	1 (0.1)
	Small intestinal obstruction	0	1 (0.1)
	Umbilical hernia	1 (0.1)	0
	Vomiting	0	1 (0.1)
General disorders and administration site conditions		3 (0.4)	1 (0.1)
	Chest pain	2 (0.3)	1 (0.1)
	Hypothermia	1 (0.1)	0
Hepatobiliary disorders		2 (0.3)	0
	Cholecystitis	1 (0.1)	0
	Cholelithiasis	1 (0.1)	0
Infections and infestations		5 (0.7)	7 (1.0)
	Appendicitis	0	2 (0.3)
	Cellulitis	0	1 (0.1)
	Gastroenteritis	1 (0.1)	1 (0.1)
	Influenza	0	1 (0.1)
	Kidney infection	1 (0.1)	0
	Localised infection	0	1 (0.1)
	Meningitis	0	1 (0.1)
	Postprocedural cellulitis	1 (0.1)	0
	Pyelonephritis	1 (0.1)	0
	Wound infection	1 (0.1)	0
Injury, poisoning and procedural complications		5 (0.7)	5 (0.7)
	Accidental overdose	1 (0.1)	0
	Ankle fracture	2 (0.3)	0
	Drug exposure during pregnancy	0	1 (0.1)
	Foot fracture	0	1 (0.1)
	Intentional overdose	0	1 (0.1)
	Joint sprain	0	1 (0.1)
	Laceration	1 (0.1)	1 (0.1)
	Patella fracture	0	1 (0.1)
	Road traffic accident	1 (0.1)	1 (0.1)
	Skin laceration	0	1 (0.1)
Metabolism and nutrition disorders		27 (3.9)	38 (5.4)
	Diabetic complication	0	1 (0.1)
	Diabetic foot	0	1 (0.1)
	Diabetic ketoacidosis	3 (0.4)	0

Table 7.1.2.1.1.2 Serious Adverse Events Occurring in Adult Type 1 Patients, Controlled Phase 2/3 Studies			
MedDRA System Organ Class	**MedDRA Preferred Event Term**	**Inh Ins total n = 698 # events (# events per 100 patients)**	**SQ total n = 705 # events (# events per 100 patients)**
	Hyperglycemia	1 (0.1)	1 (0.1)
	Hypoglycemia	23 (3.3)	35 (5.0)
	Ketoacidosis	1 (0.1)	1 (0.1)
Musculoskeletal and connective tissue disorders		1 (0.1)	2 (0.3)
	Arthralgia	1 (0.1)	0
	Back pain	0	1 (0.1)
	Intervertebral disc protrusion	0	2 (0.3)
Neoplasms, benign, malignant and unspecified, including cysts and polyps		1 (0.1)	3 (0.4)
	Breast cancer	1 (0.1)	0
	Breast cancer female	0	1 (0.1)
	Pancreatic carcinoma	0	1 (0.1)
	Uterine leiomyoma	0	1 (0.1)
Nervous system disorders		10 (1.4)	23 (3.3)
	Amnesia	0	2 (0.3)
	Aphasia	0	1 (0.1)
	Coma	0	1 (0.1)
	Convulsion	2 (0.3)	7 (1.0)
	Disturbance in attention	0	1 (0.1)
	Hypoglycemic coma	1 (0.1)	0
	Loss of consciousness	7 (1.0)	12 (1.7)
	Syncope	0	2 (0.3)
Pregnancy, puerperium and perinatal conditions		2 (0.3)	2 (0.3)
	Abortion spontaneous	1 (0.1)	0
	Pregnancy	0	1 (0.1)
	Premature labor	1 (0.1)	1 (0.1)
Psychiatric disorders		0	9 (1.3)
	Confusional state	0	1 (0.1)
	Depression	0	5 (0.7)
	Major depression	0	1 (0.1)
	Mental status change	0	2 (0.3)
	Suicidal ideation	0	1 (0.1)
Renal and urinary disorders		2 (0.3)	0
	Renal colic	1 (0.1)	0
	Urinary incontinence	1 (0.1)	0
Skin and subcutaneous disorders		0	2 (0.3)
	Hyperhidrosis	0	2 (0.3)
Total preferred event terms		71 (10.2)	114 (16.2)
Total number of cases		52 (7.4 cases per 100 patients)	73 (10.4 cases per 100 patients)
Total number of patients with SAEs		46 (6.7 patients with SAEs per 100 patients in group)	57 (8.1 patients with SAEs per 100 patients in group)
Source: Applicant's Table 6.1.1.2, ISS			

In Type 1 adult patients, no pattern emerged of a single type of serious adverse event, or grouping of serious adverse events, that occurred with significantly greater frequency among inhaled insulin group patients than among SQ patients. Pulmonary serious adverse events will be discussed separately in Dr. Seymour's review.

The clinical reviewer did not find evidence of "splitting" of terms that could mask the true incidence of certain adverse events. The following table, constructed by the clinical reviewer, groups types of event terms (accidents, injuries, acute neurologic, acute cardiovascular) which may occur during or as a result of hypoglycemic episodes.

Table 7.1.2.1.1.3 Serious Adverse Event Terms Potentially Related to Hypoglycemia, Controlled Phase 2/3 Trials[1] in Type 1 Patients

Event	Inhaled Insulin Groups (total n = 851) # events (# events x 100/ total subjects in group)	SQ Insulin Groups (total n = 853) # events (# events x 100/ total subjects in group)
Angina pectoris	1 (0.1)	0
Angina unstable	0	1 (0.1)
Chest pain	2 (0.2)	1 (0.1)
Myocardial infarction	3 (0.4)	2 (0.2)
Sinus tachycardia	0	1 (0.1)
Supraventricular tachycardia	1 (0.1)	0
Vomiting	0	1 (0.1)
Hypothermia	1 (0.1)	0
Ankle fracture	2 (0.2)	0
Foot fracture	0	1 (0.1)
Joint sprain	0	1 (0.1)
Laceration	1 (0.1)	1 (0.1)
Patella fracture	0	1 (0.1)
Road traffic accident	1 (0.1)	1 (0.1)
Skin laceration	0	1 (0.1)
Hypoglycemia	23 (2.7)	35 (4.1)
Amnesia	0	2 (0.2)
Aphasia	0	1 (0.1)
Coma	0	1 (0.1)
Convulsion	2 (0.2)	7 (0.8)
Grand mal convulsion	1 (0.1)	0
Hypoglycemic coma	1 (0.1)	0
Loss of consciousness	7 (0.8)	12 (1.4)
Syncope	0	2 (0.2)
Confusional state	0	1 (0.1)
Mental status changes	0	2 (0.2)
Hyperhidrosis	0	2 (0.2)
Total event terms conceivably related to hypoglycemia	46 (5.4)	77 (9.0)

1 includes Studies 106, 107, 1022, 1026, 1027

Event terms potentially related to hypoglycemia did not occur more frequently in Type 1 adult patients receiving inhaled insulin, and appear to have occurred less frequently numerically among inhaled insulin patients than among patients receiving SQ insulin.

7.1.2.1.2 Serious Adverse Events in Type 2 Patients

In controlled Phase 2 and Phase 3 studies in Type 2 patients, serious adverse events occurred with approximately equal frequency among inhaled insulin patients and comparator patients. In the group of all Phase 2 and Phase 3 studies SAEs occurred with approximately equal frequency

in inhaled insulin patients as they did among inhaled insulin patients in the controlled Phase 2/3 population.

Table 7.1.2.1.2.1 All-causality Serious Adverse Event Frequency in Type 2 Patients

	n	Subject-Months of Exposure (SME)	All-causality SAE Cases	All-Causality SAE Cases per 1,000 SME
Controlled Phase 2/3 Studies, Inh Ins	1,277	12,186	140	11.5
Controlled Phase 2/3 Studies, SQ	488	4,868	63	12.9
Controlled Phase 2/3 Studies, OA	644	6,452	78	12.1
All Phase 2/3 Studies, Inh Ins	1,578	30,688	386	12.5

Source: Applicant's Tables 6.1.1.3, 6.1.2.3, 6.2.1.3, 6.2.2.3, 2.2.1.1, 2.2.1.2, ISS Appendix

Myocardial infarction, chest pain, angina and hypoglycemia were the most common SAE terms among Type 2 patients. The following table lists SAE terms occurring among Type 2 patients. Because study drug exposure duration was significantly greater among inhaled insulin patients than among comparator patients, event rates are compared using exposure duration.

Table 7.1.2.1.2.2 Serious Adverse Events Occurring in Type 2 Patients, Controlled Phase 2/3 Studies

MedDRA System Organ Class	MedDRA Preferred Event Term	Inh Ins total subject-months = 12,186 # events (# events per 1,000 subject-months)	SQ total subject-months = 4,868 # events (# events per 1,000 subject-months)	OA total subject-months = 6,452 # events (# events per 1,000 subject-months)
Blood and lymphatic system disorders		1 (0.1)	1 (0.2)	0
	Anemia	1 (0.1)	1 (0.2)	0
Cardiac disorders		30 (2.5)	12 (2.5)	14 (2.2)
	Acute myocardial infarction	4 (0.3)	0	2 (0.3)
	Angina pectoris	2 (0.2)	1 (0.2)	4 (0.6)
	Angina unstable	4 (0.3)	1 (0.2)	1 (0.2)
	Arrhythmia	1 (0.1)	0	1 (0.2)
	Atrial fibrillation	0	3 (0.6)	0
	Atrial flutter	0	0	1 (0.2)
	Bradycardia	2 (0.2)	0	0
	Cardiac failure	1 (0.1)	0	0
	Cardiac failure acute	1 (0.1)	0	0
	Cardiac failure congestive	3 (0.2)	0	1 (0.2)
	Coronary artery disease	5 (0.4)	3 (0.6)	0
	Coronary artery occlusion	1 (0.1)	2 (0.4)	0
	Coronary artery stenosis	1 (0.1)	0	0
	Myocardial infarction	7 (0.6)	2 (0.4)	5 (0.8)
	Myocardial ischemia	1 (0.1)	1 (0.2)	0
	Palpitations	1 (0.1)	0	0
	Tachyarrhythmia	1 (0.1)	0	0
	Ventricular extrasystoles	1 (0.1)	0	0
	Ventricular fibrillation	1 (0.1)	0	0
	Ventricular tachycardia	1 (0.1)	0	0
Endocrine disorders		2 (0.2)	0	0
	Cushing's syndrome	1 (0.1)	0	0
	Hypothyroidism	1 (0.1)	0	0

Table 7.1.2.1.2.2 Serious Adverse Events Occurring in Type 2 Patients, Controlled Phase 2/3 Studies

MedDRA System Organ Class	MedDRA Preferred Event Term	Inh Ins total subject-months = 12,186 # events (# events per 1,000 subject-months)	SQ total subject-months = 4,868 # events (# events per 1,000 subject-months)	OA total subject-months = 6,452 # events (# events per 1,000 subject-months)
Eye disorders		1 (0.1)	0	2 (0.3)
	Cataract	1 (0.1)	0	0
	Eye movement disorder	0	0	1 (0.2)
	Optic ischemic neuropathy	0	0	1 (0.2)
Gastrointestinal disorders		12 (1.0)	7 (1.4)	11 (1.7)
	Abdominal discomfort	0	0	1 (0.2)
	Abdominal hernia	0	0	1 (0.2)
	Abdominal pain	0	0	2 (0.3)
	Abdominal pain upper	1 (0.1)	1 (0.2)	1 (0.2)
	Abdominal strangulated hernia	0	1 (0.2)	0
	Ascites	0	0	1 (0.2)
	Duodenal ulcer	0	1 (0.2)	1 (0.2)
	Dyspnea	0	0	1 (0.2)
	Esophageal hemorrhage	1 (0.1)	0	0
	Esophageal spasm	1 (0.1)	0	1 (0.2)
	Esophagitis	0	1 (0.2)	0
	Esophagitis ulcerative	0	1 (0.2)	0
	Food poisoning	0	0	1 (0.2)
	Gastric ulcer	0	0	1 (0.2)
	Gastric volvulus	0	1 (0.2)	0
	Gastritis	0	1 (0.2)	0
	Gastrointestinal gangrene	1 (0.1)	0	0
	Gastrointestinal hemorrhage	2 (0.2)	0	0
	Inguinal hernia	3 (0.2)	1 (0.2)	0
	Inguinal hernia, obstructive	1 (0.1)	0	0
	Pancreatitis	2 (0.2)	1 (0.2)	0
	Pancreatitis acute	0	0	1 (0.2)
	Small intestinal obstruction	1 (0.1)	1 (0.2)	0
	Vomiting	0	2 (0.4)	1 (0.2)
General disorders and administration site conditions		8 (0.7)	5 (1.0)	6 (0.9)
	Asthenia	0	1 (0.2)	0
	Chest pain	6 (0.5)	2 (0.4)	4 (0.6)
	Ill-defined disorder	0	0	1 (0.2)
	Noncardiac chest pain	1 (0.1)	1 (0.2)	0
	Edema peripheral	1 (0.1)	0	0
	Pain exacerbated	0	1 (0.2)	0
Hepatobiliary disorders		3 (0.2)	1 (0.2)	4 (0.6)
	Bile duct obstruction	1 (0.1)	0	0
	Biliary colic	0	0	1 (0.2)
	Cholecystitis	0	0	1 (0.2)
	Cholecystitis acute	1 (0.1)	0	1 (0.2)
	Cholelithiasis	1 (0.1)	1 (0.2)	1 (0.2)
Immune system disorders		2 (0.2)	0	0
	Drug hypersensitivity	1 (0.1)	0	0
	Hypersensitivity	1 (0.1)	0	0
Infections and infestations		20 (1.6)	9 (1.8)	4 (0.6)
	Appendicitis	2 (0.2)	0	0
	Bronchitis	2 (0.2)	0	0
	Bronchitis acute	1 (0.1)	0	0

Table 7.1.2.1.2.2 Serious Adverse Events Occurring in Type 2 Patients, Controlled Phase 2/3 Studies

MedDRA System Organ Class	MedDRA Preferred Event Term	Inh Ins total subject-months = 12,186 # events (# events per 1,000 subject-months)	SQ total subject-months = 4,868 # events (# events per 1,000 subject-months)	OA total subject-months = 6,452 # events (# events per 1,000 subject-months)
	Bronchopneumonia	1 (0.1)	0	0
	Cellulitis	4 (0.3)	3 (0.6)	0
	Diverticulitis	1 (0.1)	0	0
	Herpes zoster	1 (0.1)	0	0
	Infected insect bite	1 (0.1)	0	0
	Infected skin ulcer	0	1 (0.2)	0
	Osteomyelitis	2 (0.2)	1 (0.2)	0
	Peritonsillar abscess	1 (0.1)	0	0
	Pneumocystis carinii pneumonia	0	0	1 (0.2)
	Pneumonia	2 (0.2)	3 (0.6)	0
	Postoperative infection	0	1 (0.2)	0
	Sepsis	1 (0.1)	0	0
	Subcutaneous abscess	0	0	1 (0.2)
	Urinary tract infection	2 (0.2)	0	0
	Urosepsis	0	0	1 (0.2)
	Vulvar abscess	0	0	1 (0.2)
Injury, poisoning and procedural complications		8 (0.7)	4 (0.8)	4 (0.6)
	Accidental overdose	0	1 (0.2)	0
	Concussion	1 (0.1)	0	0
	Fall	1 (0.1)	0	0
	Foot fracture	1 (0.1)	0	0
	Hip fracture	1 (0.1)	1 (0.2)	0
	Multiple fractures	0	0	1 (0.2)
	Pelvic fracture	0	1 (0.2)	0
	Postoperative adhesion	2 (0.2)	0	0
	Rib fracture	0	2 (0.4)	1 (0.2)
	Road traffic accident	0	2 (0.4)	1 (0.2)
	Stitch abscess	0	0	1 (0.2)
	Tendon injury	1 (0.1)	0	0
	Upper limb fracture	1 (0.1)	0	0
	Wound	1 (0.1)	0	0
Investigations		7 (0.6)	14 (2.9)	4 (0.6)
	Blood glucose decreased	1 (0.1)	0	0
	Exercise electrocardiogram abnormal	1 (0.1)	0	0
	Gamma-glutamyl transferase increased	1 (0.1)	0	0
	Pulmonary function test decreased	0	0	1 (0.2)
Metabolism and nutrition disorders		7 (0.6)	14 (2.9)	4 (0.6)
	Diabetic foot	0	0	1 (0.2)
	Hyperglycemia	1 (0.1)	1 (0.2)	1 (0.2)
	Hyperkalemia	1 (0.1)	0	0
	Hypoglycemia	5 (0.4)	13 (2.7)	2 (0.3)
Musculoskeletal and connective tissue disorders		8 (0.7)	4 (0.8)	9 (1.4)
	Arthralgia	1 (0.1)	1 (0.2)	0
	Back pain	1 (0.1)	1 (0.2)	2 (0.3)
	Bunion	0	1 (0.2)	0
	Cataplexy	0	1 (0.2)	0
	Intervertebral disc	1 (0.1)	1 (0.2)	1 (0.2)

Table 7.1.2.1.2.2 Serious Adverse Events Occurring in Type 2 Patients, Controlled Phase 2/3 Studies

MedDRA System Organ Class	MedDRA Preferred Event Term	Inh Ins total subject-months = 12,186 # events (# events per 1,000 subject-months)	SQ total subject-months = 4,868 # events (# events per 1,000 subject-months)	OA total subject-months = 6,452 # events (# events per 1,000 subject-months)
	protrusion			
	Localized osteoarthritis	1 (0.1)	0	1 (0.2)
	Musculoskeletal stiffness	1 (0.1)	0	0
	Myalgia	1 (0.1)	0	0
	Myositis	0	0	1 (0.2)
	Pain in extremity	1 (0.1)	0	0
	Periarthritis	1 (0.1)	0	0
	Polymyalgia rheumatica	0	0	2 (0.3)
	Rheumatoid arthritis	1 (0.1)	0	0
	Toe deformity	0	0	2 (0.3)
Neoplasms, benign, malignant and unspecified, including cysts and polyps		13 (1.1)	5 (1.0)	4 (0.6)
	Basal cell carcinoma	1 (0.1)	0	1 (0.2)
	Blast cell crisis	1 (0.1)	0	0
	Carcinoid tumor of the stomach	0	1 (0.2)	0
	Carcinoma	1 (0.1)	0	0
	Chronic myeloid leukemia	1 (0.1)	0	0
	Colon cancer	1 (0.1)	1 (0.2)	1 (0.2)
	Colon cancer metastatic	1 (0.1)	0	0
	Esophageal carcinoma	1 (0.1)	0	0
	Lung adenocarcinoma	1 (0.1)	0	0
	Lung neoplasm malignant	0	0	1 (0.2)
	Malignant neoplasm progression	1 (0.1)	0	0
	Metastases to kidney	1 (0.1)	0	0
	Metastases to liver	2 (0.2)	0	0
	Metastases to lung	1 (0.1)	0	0
	Metastases to pancreas	1 (0.1)	0	0
	Metastatic bronchial carcinoma	1 (0.1)	0	0
	Ovarian cancer	0	1 (0.2)	1 (0.2)
	Ovarian cancer metastatic	0	1 (0.2)	0
	Prostate cancer	2 (0.2)	1 (0.2)	0
	Renal neoplasm	1 (0.1)	0	0
	Small intestine carcinoma	1 (0.1)	0	0
Nervous system disorders		18 (1.5)	10 (2.1)	12 (1.9)
	Carotid artery stenosis	1 (0.1)	0	1 (0.2)
	Carpal tunnel syndrome	0	0	2 (0.3)
	Cerebrovascular accident	1 (0.1)	2 (0.4)	2 (0.3)
	Convulsion	1 (0.1)	1 (0.2)	0
	Facial palsy	2 (0.2)	0	0
	Facial paresis	0	0	1 (0.2)
	Global amnesia	1 (0.1)	0	0
	Hydrocephalus	0	0	2 (0.3)
	Ischemic stroke	1 (0.1)	0	0
	Loss of consciousness	3 (0.2)	6 (1.2)	1 (0.2)
	Lumbar radiculopathy	1 (0.1)	0	0
	Migraine	1 (0.1)	0	0
	Multiple sclerosis	0	1 (0.2)	0
	Nerve compression	1 (0.1)	0	0
	Neuritis	1 (0.1)	0	1 (0.2)
	Syncope	1 (0.1)	0	2 (0.3)

Table 7.1.2.1.2.2 Serious Adverse Events Occurring in Type 2 Patients, Controlled Phase 2/3 Studies

MedDRA System Organ Class	MedDRA Preferred Event Term	Inh Ins total subject-months = 12,186 # events (# events per 1,000 subject-months)	SQ total subject-months = 4,868 # events (# events per 1,000 subject-months)	OA total subject-months = 6,452 # events (# events per 1,000 subject-months)
	Transient ischemic attack	3 (0.2)	1 (0.2)	0
Psychiatric disorders		2 (0.2)	7 (1.4)	1 (0.2)
	Anxiety	0	0	1 (0.2)
	Bipolar disorder	1 (0.1)	3 (0.6)	0
	Confusional state	0	1 (0.2)	0
	Depression	1 (0.1)	2 (0.4)	0
	Panic attack	0	1 (0.2)	0
Renal and urinary disorders		5 (0.4)	1 (0.2)	3
	Dysuria	1 (0.1)	0	0
	Nephrolithiasis	0	0	2 (0.3)
	Renal artery stenosis	0	0	1 (0.2)
	Renal colic	3 (0.2)	0	0
	Renal failure acute	1 (0.1)	1 (0.2)	0
Reproductive system and breast disorders		1 (0.1)	0	2 (0.3)
	Dysfunctional uterine bleeding	0	0	1 (0.2)
	Erectile dysfunction	1 (0.1)	0	0
	Uterine prolapse	0	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders		9 (0.7)	5 (1.0)	2 (0.3)
	Asthma	3 (0.2)	0	0
	Bronchospasm	1 (0.1)	0	0
	Cough	1 (0.1)	0	0
	Dyspnea	1 (0.1)	2 (0.4)	2 (0.3)
	Epistaxis	1 (0.1)	0	0
	Hypoxia	0	1 (0.2)	0
	Pneumothorax	1 (0.1)	1 (0.2)	0
	Respiratory distress	0	1 (0.2)	0
	Respiratory failure	1 (0.1)	0	0
	Vocal cord polyp	1 (0.1)	0	0
Skin and subcutaneous tissue disorders		3 (0.2)	1 (0.2)	0
	Diabetic bullosis	1 (0.1)	0	0
	Skin ulcer	2 (0.2)	1 (0.2)	0
Surgical and medical procedures		1 (0.1)	0	2 (0.3)
	Carpal tunnel decompression	0	0	1 (0.2)
	Removal of internal fixation	1 (0.1)	0	0
	Transurethral prostatectomy	0	0	1 (0.2)
Vascular disorders		6 (0.5)	1 (0.2)	3 (0.5)
	Arteriopathic disease	0	0	1 (0.2)
	Arteritis	0	0	1 (0.2)
	Deep vein thrombosis	0	1 (0.2)	0
	Hypertension	2 (0.2)	0	0
	Hypertensive crisis	1 (0.1)	0	0
	Intermittent claudication	0	0	1 (0.2)
	Orthostatic hypotension	1 (0.1)	0	0
Total preferred term events		184 (15.1)	96 (19.7)	92 (14.3)
Total number of cases		140 (11.5 cases per 1000 patient-months)	96 (19.7 cases per 1000 patient-months)	92 (14.3 cases per 1000 patient-months)
Total number of patients with		128 (10.5 patients with	49 (10.1 patients with	62 (9.6 patients with

Table 7.1.2.1.2.2 Serious Adverse Events Occurring in Type 2 Patients, Controlled Phase 2/3 Studies				
MedDRA System Organ Class	**MedDRA Preferred Event Term**	**Inh Ins total subject-months = 12,186 # events (# events per 1,000 subject-months)**	**SQ total subject-months = 4,868 # events (# events per 1,000 subject-months)**	**OA total subject-months = 6,452 # events (# events per 1,000 subject-months)**
SAEs		SAEs per 1000 patient-months)	SAEs per 1000 patient-months)	SAEs per 1000 patient-months)
Source: Applicant's Table 6.1.1.3, ISS				

The clinical reviewer grouped certain adverse event terms of interest for a total incidence rate. Term groupings of interest included:

- terms related to coronary artery disease, as macrovascular disease is the major cause of mortality among Type 2 diabetics
- hypoglycemia-related terms
- terms related to loss of consciousness and seizure, which may accompany severe hypoglycemia
- terms related to accidents and injuries, which also may accompany severe hypoglycemia
- immune system disorders, because of concern regarding insulin antibody formation in patients exposed to inhaled insulin

Pulmonary terms are also of interest; these will be discussed in Dr. Seymour's pulmonary review.

Table 7.1.2.1.2.3 Serious Adverse Event Terms of Special Interest in Type 2 Patients, Controlled Phase 2 and Phase 3 Studies			
Event Term Grouping	**Inh Ins total subject-months = 12,186 # events (# events per 1,000 subject-months)**	**SQ total subject-months = 4,868 # events (# events per 1,000 subject-months)**	**OA total subject-months = 6,452 # events (# events per 1,000 subject-months)**
Coronary artery disease terms[1]	25 (2.1)	10 (2.0)	12 (1.9)
Immune system terms[2]	2 (0.2)	0	0
Accident and injury terms[3]	6 (0.5)	6 (1.2)	3 (0.5)
Hypoglycemia terms[4]	6 (0.5)	13 (2.7)	2 (0.3)
Loss of consciousness and seizure[5]	5 (0.4)	7 (1.4)	3 (0.5)
1 Includes acute myocardial infarction, angina pectoris, angina unstable, coronary artery disease, coronary artery occlusion, coronary artery stenosis, myocardial infarction, myocardial ischemia **2 Includes drug hypersensitivity, hypersensitivity** **3 Includes concussion, fall, foot fracture, hip fracture, multiple fractures, pelvic fracture, rib fracture, road traffic accident, tendon injury, upper limb fracture** **4 Includes hypoglycemia, blood glucose decreased** **5 Includes convulsion, loss of consciousness, syncope**			

None of these groups of terms occurred with significantly higher frequency among inhaled insulin patients than among comparator patients; hypoglycemia adverse event terms occurred numerically more frequently among SQ patients than among inhaled insulin patients or OA patients.

Neoplastic events did not occur with more frequency in inhaled insulin group patients than in comparator groups. Two lung cancer events occurred in the inhaled insulin groups, and one occurred in the oral agent groups.

7.1.2.1.3 Serious Adverse Events in Pediatric Patients

A total of 331 patients <18 years of age were exposed to inhaled insulin in the development program. Of these, 153 participated in controlled Phase 2 and Phase 3 trials in Type 1 patients; there were also 147 control children who received subcutaneous insulin. At the request of DMEDP, the applicant provided comparative serious adverse event information for pediatric patients for controlled Phase 2/3 trials; the applicant chose a cut-off date of 1 Aug 03. The overall incidence of SAEs was somewhat higher for pediatric inhaled insulin patients than for pediatric SQ patients.

Table 7.1.2.1.3.1 All-causality Serious Adverse Event Frequency in Pediatric Patients (Cut-off Date 1 Aug 03)

	n	Subject-Months of Exposure (SME)	All-causality SAE Cases	All-causality SAEs per 100 pts	All-causality SAE Cases per 1,000 SME
Controlled Phase 2/3 Studies, Inh Ins	153	690	30	19.6	43.4
Controlled Phase 2/3 Studies, SQ	148	663	25	16.9	37.7

Source: Applicant's Table 4.1.1.1.1.1.2, p 2766, ISS

The following table summarizes the types of serious adverse events seen in children as of 1 Aug 03:

Table 7.1.2.1.3.2 Serious Adverse Events in Pediatric Patients, Controlled Phase 2/3 Trials, Cut-off Date 3 Aug 03

COSTART Organ System	COSTART Event Term	Inh Ins total n = 153 total SME = 690 # events (# events per 1,000 SME)	SQ total n = 148 total SME = 663 # events (# events per 1,000 SME)
Body as a whole		3 (4.3)	1 (1.5)
	Abdominal pain	1 (1.4)	0
	Accidental injury	0	1 (1.5)
	Flu syndrome	1 (1.4)	0
	Suicidal ideation	1 (1.4)	0
Digestive		1 (1.4)	2 (3.0)
	Gastritis	1 (1.4)	0
	Hematemesis	0	1 (1.5)
	Vomiting	0	1 (1.5)
Metabolic and nutritional		25 (36.2)	24 (36.2)
	Hypoglycemia	25 (36.2)	22 (33.2)
	Ketosis	1 (1.4)	2 (3.0)
Musculoskeletal		0	1 (1.5)
	Bone fracture accidental	0	1 (1.5)
Nervous		0	2 (3.0)
	Convulsion	0	2 (3.0)
Respiratory		1 (1.4)	0

Table 7.1.2.1.3.2 Serious Adverse Events in Pediatric Patients, Controlled Phase 2/3 Trials, Cut-off Date 3 Aug 03

COSTART Organ System	COSTART Event Term	Inh Ins total n = 153 total SME = 690 # events (# events per 1,000 SME)	SQ total n = 148 total SME = 663 # events (# events per 1,000 SME)
	Cough increased	1 (1.4)	0

Source: Applicant's Table 4.1.1.1.1.1.2, ISS

Hypoglycemia reported as a serious adverse event occurred somewhat more frequently among children taking inhaled insulin than among those taking SQ insulin. Otherwise, no single type of serious adverse event or grouping of adverse events occurred more frequently among pediatric patients taking inhaled insulin than among pediatric patients taking SQ only. Almost all serious adverse events among pediatric patients were related to hypoglycemia. Severe hypoglycemia was reported as a serious adverse event term more frequently among pediatric patients than among either adult Type 1or Type 2 patients. In the inhaled insulin groups, 20.3 severe hypoglycemic events were reported as severe events per 100 children, compared to 2.7 such events per 100 adult Type 1 patients. This also held true for the SQ groups, with 20.4 events/100 children and 4.1 events/100 adult Type 1 patients.

7.1.2.2 Serious Adverse Events by Patient

Due to the large size of the by-patient serious adverse event listings, the clinical reviewer placed them in Appendix 10.4. These listings include all serious adverse events by patient; separate tables are provided for Type 1, Type 2, and pediatric patients. Separate tables are also provided for comparator agents.

Hypoglycemic events warrant a few points. Because the applicant provided narratives only for serious adverse events that resulted in death or discontinuation, or were pulmonary in nature, or that were felt by the applicant to be treatment-related, many adverse events which are sometimes associated with hypoglycemia in clinical practice had no narrative or case report form to assist the clinical reviewer in determining whether these events (accidents, injuries, acute neurologic events and acute cardiac events) occurred in close proximity to a hypoglycemic event. The clinical reviewer asked Mr. Brian Green, Associate Director for Worldwide Regulatory Strategy for Pfizer, to clarify whether investigators routinely queried patients who had such events about whether the patient could have been hypoglycemic at the time of the event. On 19 Apr 05, Mr. Green replied that such events did not trigger an inquiry regarding possible hypoglycemia by the investigator at the study site. However, the applicant's Internal Safety and Risk Management Group (ISRMG) always sent a query regarding hypoglycemia (if the study site report did not include hypoglycemia information) back to the study site, for the following types of serious adverse events: loss of consciousness, syncope, seizure, accidents and injuries. For all other acute central nervous system and acute cardiac events, the ISRMG reviewed the study site's report of the event, and made a judgment about whether to query for possible hypoglycemia. It appears that the applicant made specific attempts to identify all cases of accidents, injuries, acute neurologic events and acute cardiac events that could be related to hypoglycemia; however,

event narratives were not always submitted for review in order for the clinical reviewer to confirm the absence of hypoglycemia as a contributing factor in these types of acute events. Further discussion of severe hypoglycemic events occurs later in the review, in Section 7.1.2.3.

The clinical reviewer examined all (>750) adverse event narratives that were provided. Adverse event terms used in the narratives were compared to adverse event terms used in the applicant's adverse event listings and datasets, in order to evaluate whether the applicant substituted a different name for the event, or whether the nature of the adverse event was worse than that implied by the term the applicant used. In general, the applicant's terms matched those of the narrative and those used by investigators in individual study reports very well. However, the clinical reviewer identified some serious hypoglycemic events that were accompanied by an accident or injury, in which the applicant did not include the accident or injury term in the adverse event listing. These are further discussed in Section 7.1.2.3. The by-patient serious adverse event listings in Appendix 10.4 note those SAEs for which narratives were provided, and whether the applicant's adverse event term was accurate and matched the term used by the investigator.

Dr. Seymour, DPADP clinical reviewer, will discuss pulmonary SAEs in her review. The clinical reviewer prepared a brief summary of each nonpulmonary SAE for which a narrative was provided. Because of the large number of these narratives, they appear in Appendix 10.5.

7.1.2.3 Summary of Findings from Review of Narratives

For those patients for whom serious adverse event narratives were available, the applicant's assigned event term generally matched that given by the investigator, and generally correctly indicated the nature of the event.

Information from these narratives was useful in further characterizing serious hypoglycemic adverse events.

Serious hypoglycemia is always a concern in the management of diabetes, and may be of particular concern with Exubera®
the lack of dose proportionality, a
drug-device combination could increase the risk of unpredictable and serious hypoglycemia; and in brittle patients, or patients of low body weight, could also increase the risk for diabetic ketoacidosis. Therefore, the clinical reviewer paid particular attention to both the number and the nature of serious hypoglycemic events. Numbers of serious hypoglycemic events overall have been discussed above in Section 7.1.2.1. Regarding the nature of serious hypoglycemic events, the clinical reviewer identified those events which had serious accompanying events, e.g. loss of consciousness, syncope, accidents and injuries. The incidence of these events is presented in the following table.

Table 7.1.2.3.1 Incidence of Serious Hypoglycemic Events Accompanied by Loss of Consciousness, Syncope, Accident or Injury, All Phase 2/3 Trials

Diabetes Type	Inh Ins # events (# events per 1,000 patient-months)	SQ # events (# events per 1,000 patient-months)	OA # events (# events per 1,000 patient-months)
Type 1 Adult (SME[1] inh = 16,571, SQ = 6,052)	29 (1.8)	19 (3.1)	n/a
Type 2 Adult (SME inh = 30,688, SQ = 4,868, OA = 6,453)	7 (0.2)	8 (1.6)	2 (0.3)
Type 1 Pediatric (SME inh = 6,242, SQ = 663)	12 (1.9)	2 (3.0)	n/a

1 Total subject-months of exposure

Inhaled insulin group patients do not appear to have had a higher incidence of potentially dangerous accompanying events to serious hypoglycemic episodes than did comparator patients.

Upon review of all serious hypoglycemic events narratives, the clinical reviewer noted some cases in which the event was reported only as hypoglycemia, and an accompanying accident or injury that appeared in the narrative was not mentioned in the listing. These cases are counted in the above table. The clinical reviewer was concerned that the serious adverse event listings provided by the applicant might not accurately reflect the nature of serious hypoglycemic events that occurred among inhaled insulin patients. Therefore, the clinical reviewer also reviewed all narratives provided by the applicant for serious hypoglycemic events for patients in comparator groups as well as inhaled insulin groups. The clinical reviewer then compared the hypoglycemic events noted in the applicant's serious adverse event listing (Table 6.3.1.1, Section 2.7.4) to the accompanying narratives. The following table includes patients whose narrative reported that an accident or injury accompanied their hypoglycemic event, but whose adverse event listing did not note the injury.

Table 7.1.2.3.2 Patients with Accidents or Injuries Accompanying a Serious Hypoglycemic Event, for Whom the Accident or Injury was Reported in a Narrative but not in the Applicant's Serious Adverse Event Listing[1]

Patient ID	Diabetes Type	Tx	Event Term in SAE Listing	Event from Narrative
1022-1006-0302	1	Inh Ins	Hypoglycemia	Also had accompanying motorcycle accident, clavicular rhegma
1022-1026-1489	1	Inh Ins	Hypoglycemia	Also had accompanying motor vehicle accident
1029-1093-3857	2	Inh Ins	Hypoglycemia, loss of consciousness	Also had accompanying fall and front teeth injury
106-5065-6947	1	SQ	Hypoglycemia, seizure, intentional overdose of study drug	Also had accompanying tongue biting and airway obstruction
1022-1037-2135	1	SQ	Hypoglycemia	Also had accompanying fall
1027-1016-0643	2	SQ	Hypoglycemia, loss of consciousness	Also had accompanying car accident
1029-1065-2794	2	SQ	Hypoglycemia, unconsciousness, seizure	Also had accompanying tongue laceration

1 Table 6.3.1.1, Section 2.7.4

Although the serious adverse event listings for hypoglycemic events sometimes did not include mention of an accompanying accident or injury, this reconciliation difference did not occur more

frequently among inhaled insulin patients than among comparator patients. It is possible that investigators did not consider the accident or injury as a serious event itself, and therefore did not include it. It is also possible that investigators considered the accident or injury as part of the hypoglycemic event, and therefore did not mention it separately.

Diabetic ketoacidosis is the leading cause of mortality among pediatric Type 1 diabetics (Dunger 2003, Edge 1999), and therefore is an event of significant interest. No deaths from diabetic ketoacidosis occurred in children in this development program, and no cases of cerebral edema accompanying DKA were reported; cerebral edema accounts for 57-87% of DKA deaths in children (Edge 2001, Glaser 2001). Pediatric serious adverse events of diabetic ketoacidosis did not occur more frequently among inhaled insulin patients than among SQ patients in controlled Phase 2/3 trials (one case among inhaled insulin patients, two cases among SQ patients). However, in the extension Study 111, a total of 21 serious adverse events of ketoacidosis occurred among 17 patients. This study had a large total duration of exposure for pediatric patients, with a total of 5,801 subject-months of exposure; 3.6 cases of DKA occurred per 1,000 SME. The total number of subject-months of pediatric exposure for both treatment groups in the total safety database was 6,242 patient-months (520.2 patient-years) for inhaled insulin and 663 patient-months (55.3 patient-years) for SQ. This gives comparative incidence rates of 0.04 cases of diabetic ketoacidosis per child-year for inhaled insulin patients, and 0.04 cases of DKA per child-year for SQ patients. The incidence of DKA in the overall pediatric development program does not appear to be higher for children receiving inhaled insulin than for children receiving SQ insulin. The reported incidence of DKA (after initial diagnosis) in the medical literature ranges from 1-10% per year (Dunger 2003). In Study 111, there were 483.4 child-years of exposure, and 17 patients had DKA, for an incidence of .04 cases per child-year. Although no concurrent control exists for this comparison to the medical literature, the incidence of DKA among children treated with inhaled insulin does not appear to exceed the expected incidence in the general pediatric Type 1 diabetic population.

7.1.2.4 Summary of Serious Adverse Event Findings

Among all patients in the study population, serious hypoglycemia was the most commonly reported serious adverse event. Among adult patients in general, serious hypoglycemia reported as a serious adverse event did not occur more frequently among inhaled insulin patients than among comparator patients. Hypoglycemia reported as a serious adverse event occurred somewhat more frequently among children taking inhaled insulin than among children taking SQ insulin. Severe hypoglycemia was reported as a serious adverse event term more frequently among pediatric patients than among either adult Type 1or Type 2 patients.

Pulmonary serious adverse events will be discussed in Dr. Seymour's pulmonary review. No other type of serious adverse event occurred with significantly greater frequency among inhaled insulin patients than among comparator patients. Explorations for event groupings of special interest also did not reveal an increased incidence among inhaled insulin patients.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The following tables summarize dropouts among Type 1, Type 2 and pediatric subjects:

Table 7.1.3.1.1: Summary of Dropouts among Adult Type 1 Patients, Controlled Phase 2 and Phase 3 Studies

Reason for Discontinuation	Inh Ins (n = 698) n (%)	SQ (n = 705) n (%)
Total Discontinuations	96 (13.8)	83 (11.8)
Adverse Event	22 (3.2)	6 (0.9)
Insufficient Clinical Response	10 (1.4)	3 (0.4)
Laboratory Abnormality	3 (0.4)	0
Patient Died	3 (0.4)	0
Did not Meet Entrance Criteria	0	2 (0.3)
Lost to Followup	8 (1.1)	15 (2.1)
Protocol Violation	5 (0.7)	5 (0.7)
Subject no Longer Willing to Participate in Study	29 (4.2)	30 (4.3)
Withdrawn Consent	8 (1.1)	13 (1.8)
Other	3 (0.4)	7 (1.0)
Source: Applicant's Table 7.1.1.1.2, Safety Summary pg 2365		

Table 7.1.3.1.2: Summary of Dropouts among Adult Type 1 Patients Receiving Inhaled Insulin in all Phase 2 and Phase 3 Studies

Reason for Discontinuation	Inh Ins (total n = 918) n (%)
Total Discontinuations	292 (31.8)
Adverse Event	35 (3.8)
Insufficient Clinical Response	32 (3.5)
Laboratory Abnormality	3 (0.3)
Patient Died	6 (0.7)
Lost to Followup	19 (2.1)
Protocol Violation	21 (2.3)
Subject No Longer Willing to Participate in Study	30 (3.3)
Withdrawn Consent	118 (12.9)
Withdrawn Due to Pregnancy	5 (0.5)
Source: Applicant's Table 7.2.1.1.2, Safety Summary pg 2521	

Observations of note regarding reasons for discontinuation among Type 1 diabetics include:

- In controlled trials, discontinuations due to adverse events were more common among inhaled insulin patients than among SQ patients.
- A large number of inhaled insulin patients withdrew consent during uncontrolled portions of Phase 2 and Phase 3 trials

Specific adverse events leading to discontinuation are discussed in Section 7.1.3.2.

Table 7.1.3.1.3: Summary of Dropouts among Adult Type 2 Patients, Controlled Phase 2 and Phase 3 Studies

Reason for Discontinuation	Inh Ins (n = 1,277) n (%)	SQ (n = 488) n (%)	OA (n = 644) n (%)
Total Discontinuations	163 (12.8)	64 (13.1)	93 (14.4)

Table 7.1.3.1.3: Summary of Dropouts among Adult Type 2 Patients, Controlled Phase 2 and Phase 3 Studies

Reason for Discontinuation	Inh Ins (n = 1,277) n (%)	SQ (n = 488) n (%)	OA (n = 644) n (%)
Adverse Event	46 (3.6)	9 (1.8)	21 (3.3)
Insufficient Clinical Response	8 (0.6)	3 (0.6)	10 (1.6)
Laboratory Abnormality	1 (0.1)	0	0
Patient Died	4 (0.3)	0	3 (0.5)
Did not Meet Entrance Criteria	1 (0.1)	0	4 (0.6)
Lost to Followup	8 (0.6)	11 (2.3)	7 (1.1)
Protocol Violation	14 (1.1)	10 (2.0)	9 (1.4)
Subject no Longer Willing to Participate in Study	23 (1.8)	24 (4.9)	0
Withdrawn Consent	35 (2.7)	4 (0.8)	25 (3.9)
Other	23 (1.8)	6 (1.2)	14 (2.2)
Source: Applicant's Table 7.1.1.2.0, Safety Summary pg 2366			

Table 7.1.3.1.4: Summary of Dropouts among Adult Type 2 Patients Receiving Inhaled Insulin in all Phase 2 and Phase 3 Studies

Reason for Discontinuation	Inh Ins (total n = 1578) n (%)
Total Discontinuations	452 (28.6)
Adverse Event	109 (6.9)
Insufficient Clinical Response	15 (1.0)
Laboratory Abnormality	1 (0.1)
Patient Died	12 (0.8)
Lost to Followup	41 (2.6)
Protocol Violation	46 (2.9)
Subject No Longer Willing to Participate in Study	25 (1.6)
Withdrawn Consent	134 (8.5)
Source: Applicant's Table 7.2.1.2, Safety Summary pg 2522	

Observations of note regarding reasons for discontinuation among Type 2 diabetics include:

- Discontinuations due to adverse events occurred slightly numerically more frequently among inhaled insulin patients than among SQ patients, but occurred with equal frequency between inhaled insulin patients and patients in oral agents groups.
- As noted with Type 1 patients, a large number of patients were discontinued from study for "withdrawn consent" in the uncontrolled portions of Phase 2 and Phase 3 trials.

Specific adverse events leading to discontinuation are discussed in Section 7.1.3.2.

Table 7.1.3.1.5: Summary of Dropouts among Pediatric Type 1 Patients, Controlled Phase 2 and Phase 3 Studies

Reason for Discontinuation	Inh Ins (n = 153) n (%)	SQ (n = 148) n (%)
Total Discontinuations	5 (3.3)	5 (3.4)
Adverse Event	0	0
Insufficient Clinical Response	1 (0.7)	1 (0.7)
Laboratory Abnormality	0	0
Patient Died	0	0
Did not Meet Entrance Criteria	0	0
Lost to Followup	0	1 (0.7)
Protocol Violation	1 (0.7)	1 (0.7)
Subject no Longer Willing to Participate in Study	0	0
Withdrawn Consent	3 (2.0)	2 (1.4)

Table 7.1.3.1.5: Summary of Dropouts among Pediatric Type 1 Patients, Controlled Phase 2 and Phase 3 Studies

Reason for Discontinuation	Inh Ins (n = 153) n (%)	SQ (n = 148) n (%)
Other	0	0

Source: Applicant's Table 7.1.2.1.0, Safety Summary pg 2368

The clinical reviewer was unable to locate the applicant's definition for "withdrawn consent" in the submitted NDA materials. The large number of patients for whom consent was withdrawn is of concern, because it raises the question of whether some of these patients actually dropped out for adverse events, tolerability issues, device use problems, or other noteworthy reasons. On 4 May 05, the clinical reviewer called Mr. Brian Green, Pfizer Regulatory Affairs, and asked him the following questions:

- What was the definition of "withdrawn consent"?
- What was the difference between the reasons "subject no longer willing to participate in study" and "withdrawn consent"?
- What were the reasons given by patients for withdrawal of consent?

On 10 Jun 05, Pfizer submitted responses to the above questions.

"'Withdrawn consent' was used to document a voluntary withdrawal on the part of the patient with no medical issue contributing to the discontinuation. Use of this reason would have required that the patient had expressed a desire to withdraw from the study as opposed to 'having' to withdraw from the study for other reasons (i.e. the subject moved, the subject had a scheduling conflict, etc).

The definitions of 'withdrawn consent' and 'patient no longer willing to participate in study' are the same. In early 2001, Pfizer decided to change the case report form (CRF) terminology of 'withdrawn consent' to 'subject no longer willing to participate in study'."

Pfizer stated that, for Studies 102, 103, 104, 106, 107, 108, 109, 110, 1001 and 1002, the CRF used the term "withdrawn consent", but had "no allowance for specification of reason". Pfizer provided reasons for "withdrawn consent" and "patient no longer willing to participate in study" for Studies 111, 1022, 1027, 1028, 1029 and 1030. Most of these reasons do not relate to adverse events, tolerability issues, or device problems. Some patients, however, had noteworthy reasons for withdrawal, i.e. it appears that they may actually have withdrawn for adverse events, lack of efficacy, or device concerns.

Table 7.1.3.1.6 Discontinuations for "Withdrew Consent", "No Longer Willing to Participate" and "Other" that May Actually Have Been Due to Adverse Events, Lack of Efficacy, or Device Concerns

Patient ID	Study	Tx Grp	Original Listed Category of Discontinuation	Reason for Withdrawal Given in Applicant's 10 Jun 05 Submission
106-5002-6848	111	Inh ins	Withdrew consent	patient felt blood sugars were erratic and hard to control
106-5021-6166	111	Inh ins	Withdrew consent	"pt wanted more consistent control preferred previous insulin regimen"

Table 7.1.3.1.6 Discontinuations for "Withdrew Consent", "No Longer Willing to Participate" and "Other" that May Actually Have Been Due to Adverse Events, Lack of Efficacy, or Device Concerns

Patient ID	Study	Tx Grp	Original Listed Category of Discontinuation	Reason for Withdrawal Given in Applicant's 10 Jun 05 Submission
106-5040-6575	111	Inh ins	Withdrew consent	"felt he could get better glucose control on SQ regimen"
106-5044-6270	111	Inh ins	Withdrew consent	"didn't have enough control of diabetes on Exubera"
106-5044-6276	111	Inh ins	Withdrew consent	lack of efficacy
106-5047-6553	111	Inh ins	Withdrew consent	insufficient clinical response
106-5055-6133	111	Inh ins	Withdrew consent	"pt wants definitive tx"
106-5055-6621	111	Inh ins	Withdrew consent	"pt wanted definitive tx"
106-5059-6679	111	Inh ins	Withdrew consent	poor blood glucose control
106-5062-6209	111	Inh ins	Withdrew consent	"poor glycemic control and future protocol changes"
106-5064-6104	111	Inh ins	Withdrew consent	suboptimal blood glucose control
107-5005-7687	111	Inh ins	Withdrew consent	subject unhappy with HbA1c results
107-5007-7985	111	Inh ins	Withdrew consent	subject unhappy with efficacy of inhaled insulin
107-5010-7610	111	Inh ins	Withdrew consent	pt believed she had better glucose control on pump
107-5010-7615	111	Inh ins	Withdrew consent	pt feels she has inadequate control of dosing of inhaled insulin
107-5066-7742	111	Inh ins	Withdrew consent	insufficient clinical response
107-5066-7744	111	Inh ins	Withdrew consent	insufficient clinical response
107-5066-7745	111	Inh ins	Withdrew consent	poor blood sugar control
107-5088-7030	111	Inh ins	Withdrew consent	no longer interested, unhappy with diabetes control
107-5095-7485	111	Inh ins	Withdrew consent	poor control of blood sugars
107-5095-7487	111	Inh ins	Withdrew consent	poor glucose control
108-5055-8539	111	Inh ins	Withdrew consent	pt wants definitive tx
109-5020-0245	111	Inh ins	Withdrew consent	"did not feel receiving any benefit from study drug"
1022-1022-1255	1022	Inh ins	No longer willing to participate	subject's blood sugar control declined after randomization
1022-1037-2140	1022	Inh ins	No longer willing to participate	subject felt "it was just not working"
1022-1042-2437	1022	Inh ins	No longer willing to participate	pt feels she was under better blood sugar control prior to inhaled insulin treatment
1022-1046-2670	1022	Inh ins	No longer willing to participate	subject felt that Exubera inadequately controlled his sugars
1022-5155-3738	1022	Inh ins	No longer willing to participate	pt feels blood glucose levels were better on SQ insulin
1028-1001-0395	1028	Inh ins	No longer willing to participate	pt's blood sugar control was not acceptable, pt unhappy with the results
1028-1050-4769	1028	Inh ins	No longer willing to participate	subject felt glucose not controlled well enough
1029-1029-0780	1029	Inh ins	No longer willing to participate	insufficient clinical response
1029-1079-	1029	Inh ins	No longer willing to participate	pt was not satisfied with blood glucose control

Table 7.1.3.1.6 Discontinuations for "Withdrew Consent", "No Longer Willing to Participate" and "Other" that May Actually Have Been Due to Adverse Events, Lack of Efficacy, or Device Concerns

Patient ID	Study	Tx Grp	Original Listed Category of Discontinuation	Reason for Withdrawal Given in Applicant's 10 Jun 05 Submission
3262				
1029-1100-3320	1029	SQ	No longer willing to participate	"pt started himself back on oral antihyperglycemic agents due to elevated BGs"
1029-1115-5395	1029	SQ	No longer willing to participate	"Pt too stressed out over slightly elevated BG levels."
107-5010-7614	111	Inh ins	Withdrew consent	device large, cumbersome
107-5063-7419	111	Inh ins	Withdrew consent	device clumsy and conspicuous
107-5067-7759	111	Inh ins	Withdrew consent	inhaler too bulky to carry around while traveling
107-5098-7514	111	Inh ins	Withdrew consent	"device too big, blister mg's do not allow for fine adjustment"
107-5127-7219	111	Inh ins	Other	"patient finds inhaler an inconvenient size"
107-5127-7774	111	Inh ins	Other	"inconvenience of inhaler"
108-5060-8437	111	Inh ins	Withdrew consent	subject finds device too big
107-5083-7499	111	Inh ins	Withdrew consent	frequent hypoglycemic episodes
107-5102-7144	111	Inh ins	Withdrew consent	frequent hypoglycemic episodes and concern about elevated insulin antibodies
107-5127-7221	111	Inh ins	Other	"too many serious hypoglycemias (sic) caused by the study drug"
1001-0133-3332	1001	Inh ins	Other	hs and early a.m. low blood sugars
1022-1031-1789	1022	Inh ins	No longer willing to participate	"Subject was not 'comfortable' with inhaled insulin. He felt he was having more hypoglycemic events. In reality he was not, but he was just really uncomfortable so he withdrew."
1022-1038-2194	1022	Inh ins	No longer willing to participate	subject with middle of the night lows despite lowering Lantus
1022-1038-2195	1022	Inh ins	No longer willing to participate	"subject felt Exubera did not adequately bring down his high BG and having too many hypos"
1028-1048-4574	1028	Inh ins	No longer willing to participate	experienced hypoglycemic events and was unable to self-treat
1029-1047-2431	1029	Inh ins	No longer willing to participate	"hypoglycemic events- numbness to mouth, tongue and lips"
1029-1065-2791	1029	Inh ins	No longer willing to participate	recurrent hypoglycemic reactions
107-5066-7741	111	Inh ins	Other	PFT abnormalities
109-5052-0408	111	Inh ins	Other	worsening of PFTs
1002-0069-5134	1002	Inh Ins	Other	decrease in PFT results
1002-0127-5251	1002	OA	Other	DLco <75% predicted
1029-1048-2491	1029	Inh ins	Other	PFTs >15% decrease from baseline
1029-1111-4859	1029	Inh ins	Other	decline in FEV1
107-5102-7639	111	Inh ins	Withdrew consent	pt concerned about elevated insulin antibodies
1026-1001-0034	1026	Inh ins	No longer willing to participate	psychological problems
1027-1028-1628	1027	Inh ins	No longer willing to participate	depression
1028-1024-	1028	Inh ins	No longer willing to participate	diarrhea

Table 7.1.3.1.6 Discontinuations for "Withdrew Consent", "No Longer Willing to Participate" and "Other" that May Actually Have Been Due to Adverse Events, Lack of Efficacy, or Device Concerns

Patient ID	Study	Tx Grp	Original Listed Category of Discontinuation	Reason for Withdrawal Given in Applicant's 10 Jun 05 Submission
2193				
1028-1056-5367	1028	Inh ins	No longer willing to participate	not able to return for clinic visit due to broken leg
1029-1010-0366	1029	Inh ins	No longer willing to participate	"pt feels that he needs to recuperate after the Herpes infection and concentrate on getting better"
1029-1074-3141	1029	Inh ins	No longer willing to participate	"pt feels lousy and dizzy all the time"
1029-1059-2615	1029	SQ	No longer willing to participate	"pt no longer want the obligation of continuing in the study and wants to focus on his last SAE"

These revised reasons for withdrawal have some impact on the profile of reasons for discontinuation from study.

Study 111 was an uncontrolled extension study, and thus had no control group for comparisons of rates. However, review of these revised reasons changes the following data for reasons for discontinuation for inhaled insulin patients in all Phase 2/3 trials:

Table 7.1.3.1.7 Comparison of Original and Revised Reasons for Discontinuation, All Phase 2/3 Studies, Inhaled Insulin Patients

Diabetes Type	Reason for Discontinuation	Original n (%)	Revised n (%)
1 (total n = 918)	Adverse Event	35 (3.8)	44 (4.8)
	Insufficient Clinical Response	32 (3.5)	58 (6.3)
	Device Concerns	n/a	6 (0.7)
2 (total n = 1578)	Adverse Event	109 (6.9)	119 (7.5)
	Insufficient Clinical Response	15 (1.0)	20 (1.3)
	Device Concerns	n/a	1 (0.1)

This revision appears to increase the percentage of Type 1 diabetics who withdrew for insufficient clinical response in the population of all Phase 2/3 trials. However, one cannot conclude on the basis of uncontrolled data that misrepresentation of reasons for discontinuation occurred.

The following table details the effect of the revisions on the reasons for discontinuation for controlled studies. Revised data for Study 1028 were not included, because diabetes type was not listed in the study report for the affected patients.

Table 7.1.3.1.8 Comparison of Original and Revised Reasons for Discontinuation, Controlled Phase 2/3 Studies

		Inh Ins Type 1 n = 698 Type 2 n = 1277		SQ Type 1 n = 705 Type 2 n = 488		OA Type 1 n = 0 Type 2 n = 644	
Diabetes Type	**Reason for Discontinuation**	**Original n (%)**	**Revised n (%)**	**Original n (%)**	**Revised n (%)**	**Original n (%)**	**Revised n (%)**
1	Adverse Event	22 (3.2)	26 (3.7)	6 (0.9)	same	n/a	n/a
	Insufficient Clinical Response	10 (1.4)	15 (2.1)	3 (0.4)	same	n/a	n/a

Table 7.1.3.1.8 Comparison of Original and Revised Reasons for Discontinuation, Controlled Phase 2/3 Studies

		Inh Ins Type 1 n = 698 Type 2 n = 1277		SQ Type 1 n = 705 Type 2 n = 488		OA Type 1 n = 0 Type 2 n = 644	
Diabetes Type	**Reason for Discontinuation**	**Original n (%)**	**Revised n (%)**	**Original n (%)**	**Revised n (%)**	**Original n (%)**	**Revised n (%)**
2	Adverse Event	46 (3.6)	55 (4.3)	9 (1.8)	10 (2.0)	21 (3.3)	22 (3.4)
	Insufficient Clinical Response	8 (0.6)	10 (0.8)	3 (0.6)	5 (1.0)	10 (1.6)	same

If investigators were unclear on how reasons for discontinuation should have been classified, one would expect that they would have misclassified reasons with approximately equal frequency in inhaled insulin and control groups. However, discontinuations due to adverse events and insufficient clinical response appear to have been misclassified more frequently for inhaled insulin patients than for comparator patients in the controlled Phase 2/3 population. Because revised discontinuation data were available for only a few of the controlled trials, the overall effect might be diluted. The following table compares the original and revised reasons for discontinuation for those trials for which revised data were available.

Table 7.1.3.1.9 Comparison of Original and Revised Reasons for Discontinuation, Controlled Phase 2/3 Studies for Which Revised Discontinuation Data Were Available[1]

		Inh Ins Type 1 n = 425 Type 2 n = 538		SQ Type 1 n = 430 Type 2 n = 314		OA Type 1 n = 0 Type 2 n = 201	
Diabetes Type	**Reason for Discontinuation**	**Original n (%)**	**Revised n (%)**	**Original n (%)**	**Revised n (%)**	**Original n (%)**	**Revised n (%)**
1	Adverse Event	9 (2.1)	13 (3.1)	3 (0.7)	same	n/a	n/a
	Insufficient Clinical Response	7 (1.6)	12 (2.8)	0	same	n/a	n/a
2	Adverse Event	24 (4.5)	33 (6.1)	4 (1.3)	5 (1.6)	7 (3.5)	8 (4.0)
	Insufficient Clinical Response	4 (0.7)	6 (1.1)	3 (1.0)	5 (1.6)	2 (1.0)	same

1 Includes Studies 1001, 1022, 1026, 1027 and 1029

When considering the group of those studies for which revised data for reasons for discontinuation were available, the apparently more frequent misclassification of discontinuation reasons among inhaled insulin patients led to greater differences between groups in the rates of discontinuation for:

- adverse events (greater difference in frequency for both Type 1 and Type 2)
- insufficient clinical response (greater difference in frequency for Type 1)

This disparity in rates of apparent misclassification of reasons for discontinuation cannot be completely explained, but raises a question of investigator reporting bias for these studies. These trials included about 60% of the Type 1 patients in the controlled Phase 2/3 population, and about 40% of Type 2 patients in controlled Phase 2/3 trials. Inability to obtain revised data for the remaining clinical trials leaves unanswered the question of whether this was a pervasive problem. However, because many of the study centers participated in multiple trials, it is

possible that misclassification also occurred in trials other than those for which revised reasons for discontinuation were available.

Analysis of demographic data (age, gender and race) for permanent discontinuations revealed few differences by demography. Among Type 1 patients, older patients (ages 45-64 years) in inhaled insulin groups were more likely to discontinue study than younger patients (ages 18-44) in inhaled insulin groups. Older inhaled insulin group patients (ages 45-64) were more likely to discontinue study than SQ group patients in the same age range [37/190 (19.5%) vs 19/196 (9.7%)]. Among older Type 2 diabetics (ages 65-74), inhaled insulin group patients were somewhat more likely to discontinue study than comparator patients [inh ins 46/264 (17.4%), SQ 14/102 (13.7%), OA 15/122 (12.3%)]. Little difference existed between groups by gender. Few non-Caucasian subjects participated in the development program, and no clear differences emerged among discontinuation rates or reasons. Sources for demographic data for discontinuations included the applicant's Tables 7.1.2.1.0, 7.1.3.1, 7.1.4.1, 7.1.2.2.0, 7.1.3.2, and 7.1.4.2 in the safety summary.

Temporary discontinuations due to adverse events were more common among Type 1 inhaled insulin patients than among Type 1 patients in SQ groups. For adult Type 1 patients in controlled Phase 2 and Phase 3 trials, 4.7% of inhaled insulin patients had temporary discontinuations due to adverse events, compared to 1.3% of SQ patients. The most common category of adverse events leading to temporary discontinuation among Type 1 diabetic inhaled insulin patients was respiratory, with 16 such events among inhaled insulin patients vs 1 such event in the SQ groups.

Temporary discontinuations due to adverse events were more common among Type 2 inhaled insulin patients (5.6% of patients) compared to Type 2 SQ group patients (1.6% of patients), but occurred with comparable frequency in patients in oral agent groups (6.8%). Again, the most common category of event leading to temporary discontinuation was respiratory, with 24 Type 2 subjects (1.9%) temporarily discontinuing inhaled insulin for respiratory reasons, vs 1 respiratory temporary discontinuation among SQ patients, and zero among oral agent patients. Temporary discontinuations due to hypoglycemia were also more common among Type 2 inhaled insulin patients, with 14 patients (1.1%) temporarily discontinuing due to hypoglycemia, vs 3 (0.6%) and 3 (0.5%) of SQ and oral agent patients, respectively. Temporary discontinuations due to digestive events, particularly diarrhea, occurred more frequently among Type 2 oral agent group patients.

Information regarding temporary discontinuations among pediatric patients across the entire development program was not included in the NDA. In Study A2171009, a pediatric study involving 121 patients, 61 of whom were exposed to inhaled insulin, a single temporary discontinuation occurred. This occurred in an inhaled insulin group child, and was due to an upper respiratory tract infection.

7.1.3.2 Adverse events associated with dropouts

The following tables summarize adverse events leading to dropout:

Table 7.1.3.2.1 Adverse Events Resulting in Discontinuation of Type 1 Diabetics in Controlled Phase 2 and Phase 3 Studies

		Inh Ins	SQ
Total n each tx grp		**698**	**705**
Total subject-months		**5894**	**6052**
Total n d/c due to AEs		**20 (2.9%)**	**6 (0.9%)**
Body System	**COSTART AE Term**	**Inh Ins n (%)**	**Inh Ins n (%)**
Body as a Whole		3 (0.4)	1 (0.1)
	Abdominal pain	1 (0.1)	0
	Accidental injury	0	1 (0.1)
	Asthenia	1 (0.1)	0
	Lab test abnormal	1 (0.1)	0
Cardiovascular		1 (0.1)	0
	Angina pectoris	1 (0.1)	0
Digestive		0	1 (0.1)
	Gastrointestinal carcinoma	0	1 (0.1)
Metabolic and Nutritional		2 (0.3)	1 (0.1)
	Diabetic coma	1 (0.1)	0
	Hypoglycemia	2 (0.3)	1 (0.1)
Musculoskeletal		0	2 (0.3)
	Bone fracture accidental	0	1 (0.1)
	Myalgia	0	1 (0.1)
Nervous		2 (0.3)	0
	Anxiety	1 (0.1)	0
	Neuropathy	1 (0.1)	0
Respiratory		11 (1.6)	0
	Asthma	1 (0.1)	0
	Cough increased	7 (1.0)	0
	Dyspnea	3 (0.4)	0
	Laryngitis	1 (0.1)	0
	Pharyngitis	2 (0.3)	0
	Respiratory disorder	2 (0.3)	0
	Respiratory tract infection	1 (0.1)	0
	Sinusitis	1 (0.1)	0
	Sputum increased	1 (0.1)	0
Special Senses		1 (0.1)	0
	Eye hemorrhage	1 (0.1)	0
Urogenital		1 (0.1)	0
	Breast carcinoma	1 (0.1)	0

Source: Applicant's Table 7.1.5.1, Safety Summary pg 2379

In controlled Phase 2 and Phase 3 studies in Type 1 diabetics, the most common category of events leading to discontinuation was respiratory, and all discontinuations due to respiratory adverse events occurred in inhaled insulin group patients. When considering all Phase 2 and Phase 3 trials, both controlled and uncontrolled, respiratory events were again the most common category of adverse events leading to discontinuation, with a total of 21 (2.3%) of inhaled insulin group patients discontinuing due to respiratory AEs. Cough was the most common AE leading to discontinuation, accounting for 10 discontinuations (1.1% of all Ph 2/3 Type 1 patients).

When data are added from the revisions to the reasons for discontinuations submitted by the applicant on 10 Jun 05, information regarding adverse events leading to discontinuations among

Type 1 patients in controlled Phase 2/3 trials changes somewhat. Three additional discontinuations due to hypoglycemia appear to have occurred in inhaled insulin patients, for a total of 5 cases (0.7 discontinuations due to hypoglycemia per 100 inhaled insulin patients). No additional cases of discontinuation due to hypoglycemia were found in SQ patients; one case had originally been reported (0.1 discontinuations due to hypoglycemia per 100 SQ patients).

Table 7.1.3.2.2 Adverse Events Resulting in Discontinuation of Type 2 Diabetics in Controlled Phase 2 and Phase 3 Studies

		Inh Ins	SQ	OA
Total n each tx grp		**1277**	**488**	**644**
Total subject-months		**12186**	**4868**	**6452**
Total n d/c due to AEs		**15**	**3**	**11**
Body System	**COSTART AE Term**	**Inh Ins n (%)**	**SQ n (%)**	**OA n (%)**
Body as a whole		8 (0.6)	1 (0.2)	5 (0.8)
	Abdominal pain	1 (0.1)	0	2 (0.3)
	Accidental injury	1 (0.1)	0	0
	Ascites	0	0	1 (0.2)
	Back pain	1 (0.1)	0	1 (0.2)
	Chest pain	1 (0.1)	0	1 (0.2)
	Flu syndrome	1 (0.1)	0	0
	Headache	3 (0.2)	0	1 (0.2)
	Motor vehicle accident	0	1 (0.2)	0
	Neoplasm	1 (0.1)	0	0
Cardiovascular		2 (0.2)	1 (0.2)	6 (0.9)
	Bradycardia	1 (0.1)	0	0
	Cerebrovascular accident	1 (0.1)	0	1 (0.2)
	Congestive heart failure	0	0	1 (0.2)
	Heart failure	1 (0.1)	0	0
	Myocardial infarct	1 (0.1)	0	3 (0.5)
	Myocardial ischemia	1 (0.1)	1 (0.2)	1 (0.2)
	Tachycardia	0	0	1 (0.2)
	Ventricular arrhythmia	1 (0.1)	0	0
Gastrointestinal		5 (0.4)	1 (0.2)	5 (0.8)
	Diarrhea	0	0	4 (0.6)
	Duodenal ulcer	0	0	1 (0.2)
	Dyspepsia	0	0	1 (0.2)
	Gastroenteritis	1 (0.1)	0	0
	Gastrointestinal carcinoma	0	1 (0.2)	0
	Gingivitis	1 (0.1)	0	0
	Glossitis	1 (0.1)	0	0
	Nausea	2 (0.2)	0	1 (0.2)
	Pancreatitis	1 (0.1)	0	0
	Stomach ulcer	0	0	1 (0.20
Hemic and lymphatic		1 (0.1)	0	0
	Chronic myelocytic leukemia	1 (0.1)	0	0
Metabolic and nutritional		2 (0.2)	0	2 (0.3)
	Hyperglycemia	1 (0.1)	0	0
	Peripheral edema	0	0	1 (0.2)
	SGPT increased	0	0	1 (0.2)
	Wt gain	1 (0.1)	0	0
Musculoskeletal		0	1 (0.2)	1 (0.2)
	Leg cramps	0	1 (0.2)	0
	Myalgia	0	0	1 (0.2)
Nervous		3 (0.2)	0	0
	Amnesia	1 (0.1)	0	0

Table 7.1.3.2.2 Adverse Events Resulting in Discontinuation of Type 2 Diabetics in Controlled Phase 2 and Phase 3 Studies

		Inh Ins	SQ	OA
Total n each tx grp		**1277**	**488**	**644**
Total subject-months		**12186**	**4868**	**6452**
Total n d/c due to AEs		**15**	**3**	**11**
Body System	**COSTART AE Term**	**Inh Ins n (%)**	**SQ n (%)**	**OA n (%)**
	Anxiety	1 (0.1)	0	0
	Dizziness	1 (0.1)	0	0
Respiratory		28 (2.2)	0	2 (0.3)
	Asthma	7 (0.5)	0	0
	Bronchitis	3 (0.2)	0	0
	Carcinoma of lung	1 (0.1)	0	1 (0.2)
	Cough increased	13 (1.0)	0	0
	Dyspnea	5 (0.4)	0	1 (0.2)
	Pharyngitis	1 (0.1)	0	0
	Respiratory disorder	2 (0.2)	0	0
	Respiratory tract infection	3 (0.2)	0	0
	Sputum increased	1 (0.1)	0	0
Skin and appendages		1 (0.1)	0	1 (0.2)
	Sweating	1 (0.1)	0	1 (0.2)
Special senses		1 (0.1)	0	1 (0.2)
	Abnormal vision	0	0	1 (0.2)
	Retinal disorder	1 (0.1)	0	0
Urogenital		2 (0.2)	1 (0.2)	2 (0.3)
	Acute kidney failure	1 (0.1)	0	0
	Kidney function abnormal	0	0	2 (0.3)
	Prostatic carcinoma	1 (0.1)	1 (0.3)	0

Source: Applicant's Table 7.1.5.2, Safety Summary pg 2381

In controlled Phase 2 and Phase 3 studies in Type 2 diabetics, the most common category of events leading to discontinuation was respiratory, and 26/28 discontinuations due to respiratory adverse events occurred in inhaled insulin group patients. When considering all Phase 2 and Phase 3 trials, both controlled and uncontrolled, respiratory events were again the most common category of adverse events leading to discontinuation, with a total of 42 (3.9%) of inhaled insulin group patients discontinuing due to respiratory AEs (Source Applicant's Table 7.2.2.2, safety summary pg 2527). Cough was the most common AE leading to discontinuation, accounting for 26 discontinuations (1.6% of all Ph 2/3 Type 2 patients). Three events of oropharyngeal irritation (glossitis, gingivitis, pharyngitis) resulted in discontinuation in controlled Phase 2/3 trials in inhaled insulin patients, with one additional discontinuation due to pharyngitis in extension trials. No discontinuations due to oropharyngeal irritation occurred in SQ or oral agent control patients.

When data are added from the revisions to the reasons for discontinuations submitted by the applicant on 10 Jun 05, information regarding adverse events leading to discontinuations among Type 2 patients in controlled Phase 2/3 trials changes somewhat. Three discontinuations due to hypoglycemia, and three discontinuations due to abnormal PFTs, appear to have occurred in inhaled insulin patients, compared to zero in each of the comparator groups.

In controlled Phase 2 and Phase 3 trials in Type 2 diabetics, discontinuations due to neoplasia did not occur more frequently among inhaled insulin group patients than among control patients. One case of lung carcinoma occurred in the inhaled insulin groups, and one in the oral agent groups. For all Phase 2 and Phase 3 trials, controlled and uncontrolled, neoplastic adverse event terms leading to discontinuation were numerically more frequent and slightly (not statistically significantly) more frequent on a person-time basis in the inhaled insulin groups than in the control groups, as illustrated in the following table:

Table 7.1.3.2.3 Neoplastic Adverse Events Leading to Discontinuation, All Phase 2 and Phase 3 Trials in Type 2 Diabetics

	Inh Ins	SQ	OA
Total Subject-years	**1016**	**406**	**538**
COSTART Event Term	**# events (# events/ 100 subject-yrs)**	**# events (# events/ 100 subject-yrs)**	**# events (# events/ 100 subject-yrs)**
Carcinoma	1 (0.1)	0	0
Lymphoma malignant	1 (0.1)	0	0
Neoplasm	1 (0.1)	0	0
Gastrointestinal carcinoma	1 (0.1)	1 (0.2)	0
Chronic myelogenous leukemia	1 (0.1)	0	0
Carcinoma lung	3 (0.3)	0	1 (0.2)
Prostate carcinoma	1 (0.1)	1 (0.1)	0
Renal carcinoma	1 (0.1)	0	0
Total neoplastic events leading to discontinuation	10 (1.0)	2 (0.5)	1 (0.2)

Source: Applicant's Tables 7.2.2.2 and 7.1.5.2, safety summary

Insulin is a growth factor, and concern has been expressed regarding the potential for promotion of tumor formation or growth. However, this is a small difference in discontinuations due to neoplastic events, and neoplastic events (whether reported as leading to discontinuation or not) did not occur with greater frequency among inhaled insulin group patients.

In summary, permanent discontinuations from controlled Phase 2 and Phase 3 studies were slightly more common for adult Type 1 patients in inhaled insulin groups than among Type 1 patients in SQ groups. Permanent discontinuation rates were comparable for Type 2 patients between inhaled insulin, SQ insulin, and oral agent groups. Large numbers of patients withdrew consent during the uncontrolled portions of Phase 2 and Phase 3 trials for both Type 1 and Type 2 diabetics. Reasons for withdrawal of consent were not included in the original NDA submission. Upon request, the applicant provided a separate submission containing the actual wording for the reasons for discontinuation for trials which included about 60% of Type 1 patients and 40% of Type 2 patients in the Phase 2/3 controlled trial population. Review of these revised reasons for discontinuation revealed that some of those patients that were listed as having discontinued study due to "withdrawn consent", "patient no longer willing to participate", or "other", actually withdrew due to adverse events, lack of efficacy, or device concerns. This apparent misclassification of reasons for discontinuation was more common among inhaled insulin group patients than among comparator group patients. The reason for this difference between groups is unclear, but it raises a question of investigator reporting bias favoring inhaled insulin.

The most common category of adverse event leading to discontinuation among inhaled insulin group patients (both Type 1 and Type 2) was respiratory; withdrawals due to respiratory adverse events were rare among comparator group patients. The most common single adverse event leading to permanent discontinuation was cough; this reason for discontinuation occurred exclusively among inhaled insulin group patients. Permanent discontinuations due to neoplastic adverse events occurred slightly (not statistically significantly) more frequently on a person-time basis among Type 2 inhaled insulin group patients than among comparator group patients in the set of all Phase 2 and Phase 3 studies. Addition of adverse event data from the applicant's 10 Jun 05 submission regarding revised reasons for discontinuation led to a higher percentage of discontinuations for hypoglycemia among inhaled insulin patients compared to SQ patients (both Type 1 and Type 2). Temporary discontinuations for adverse events were more common among inhaled insulin patients than among SQ group patients for both Type 1 and Type 2 patients, and the most common category of adverse events leading to temporary discontinuation was respiratory.

7.1.3.3 Other significant adverse events

7.1.3.3.1 Hypoglycemic Events Identified by Specified Definitions

The review includes three general types of severe hypoglycemic events; those that were reported by investigators as serious adverse events per se, and those that were identified by either of two specific definitions.

Within most *individual studies*, there was a protocol definition of severe hypoglycemia; in order for the event to be classified as severe, patient had to meet all three of the following criteria:

- patient unable to treat themselves
- patient exhibited at least one of the following- memory loss, confusion, uncontrollable behavior, irrational behavior, unusual difficulty in awakening, suspected seizure, seizure, loss of consciousness
- measured BG ≤ 49 mg/dL; or if no BG measured, clinical manifestations reversed by oral carbohydrates, subcutaneous glucagon, or intravenous glucose

Severe hypoglycemia defined in this way was evaluated as a secondary outcome variable in the major trials.

For purposes of the *overall safety review*, severe hypoglycemic events were defined as those in which the subject had a measured blood glucose of ≤ 36 mg/dL and/or required assistance. The specified blood glucose level was requested by FDA.

The frequency of these specifically defined events may differ from the frequency of hypoglycemic events that were reported as common adverse events or serious adverse events; investigators may not have always followed the same definition for adverse event reporting as was used for the secondary outcome variable hypoglycemia definition. This section deals with specifically defined hypoglycemia. Hypoglycemic events that were reported as adverse events or serious adverse events are discussed in Sections 7.1.2 and 7.1.5.

7.1.3.3.1.1 Specifically-defined Hypoglycemic Events among Adult Type 1 Patients

Among all severe hypoglycemic events (using the overall safety definition of hypoglycemia) in Type 1 patients, 94% met the criterion of blood glucose ≤ 36 mg/dL. The occurrence of these events is summarized in the following tables.

Table 7.1.3.3.1.1.1 Severe[1] Hypoglycemic Event Rates, Adult Type 1 Patients, Phase 2 and Phase 3 Trials[2]

	Inhaled Insulin Groups	SQ Groups
Total number patients in group	691	686
Total number subject-months for group	4931.1	5102.3
Number and percent of patients with at least one severe hypoglycemic event	547 (79.2%)	533 (77.7%)
Total number of severe hypoglycemic events in group	5134	5515
Event rate (number of events per subject-month)	1.041	1.081
Risk ratio (95% CI)	0.95 (0.91-0.98)	

1 includes Studies 102, 106, 107, 1022IA, 1026, 1027
2 defined as blood glucose ≤ 36 mg/dL or requiring assistance
Source: Applicant's Table 17, Section 2.7.3.3.2.1.6, pg 35

For adult Type 1 patients overall, inhaled insulin was not associated with a higher rate of severe hypoglycemia (using the overall safety definition) than the rate seen with SQ insulin. However, in Study 107, the "intensive control" study in Type 1 diabetics, the applicant reported that severe hypoglycemic events (using the individual study definition) did occur more frequently in the inhaled insulin group than in the SQ only group. This is a potentially important finding, because intensive control is now the standard of care for Type 1 diabetics, and severe hypoglycemia tends to be the limiting factor in achieving tight control. Severe hypoglycemia can be associated with higher rates of accidents, injuries and other acute serious adverse events. If a new treatment for Type 1 diabetes is noninferior, but not superior, in efficacy to the standard of care of intensive subcutaneous insulin management, the new treatment's rate of severe hypoglycemia should not be significantly higher than that seen with the standard of care. That, however, did not appear to be the case in Study 107, where inhaled insulin was noninferior (but not superior) to subcutaneous insulin in efficacy, but had a higher rate of severe hypoglycemic events.

Table 7.1.3.3.1.1.2 Severe[1] Hypoglycemic Event Rates, ITT[2] Population, Study 107

	Inh Ins	SQ Only
Total number of patients	162	162
Total number (and percentage) of patients with any severe hypoglycemic event	26 (16.0)	22 (13.6)
Total number of severe hypoglycemic events	59	29
Total patient-months	905.4	895.5
Event rate (# events/100 patient-months)	6.5	3.2

Treatment comparison, inhaled/subcutaneous: Risk Ratio 2.02 (95% CI limits 1.30, 3.15)

1 In order to be classified as severe, patient had to meet all three of the following criteria:
- **patient unable to treat themselves**
- **patient exhibited at least one of the following- memory loss, confusion, uncontrollable behavior, irrational behavior, unusual difficulty in awakening, suspected seizure, seizure, loss of consciousness**
- **measured BG ≤ 49 mg/dL; or if no BG measured, clinical manifestations reversed by oral carbohydrates, subcutaneous glucagon, or intravenous glucose**

2 ITT population included both adult and adolescent patients

Table 7.1.3.3.1.1.2 Severe[1] Hypoglycemic Event Rates, ITT[2] Population, Study 107		
	Inh Ins	**SQ Only**
Source: Applicant's Table 5.4.2.1, Study 107 report		

It should also be noted that Study 107 excluded patients who had had two or more severe hypoglycemic episodes within the six months prior to study entry. Thus, the study did not include patients with a known predisposition to frequent severe hypoglycemia.

However, it should also be noted that the FDA Biostatistics reviewer has called into question the statistical model used by Pfizer for comparison of hypoglycemic event rates. Reanalysis is ongoing, but it appears that a more appropriate model may show that severe hypoglycemic event rates did not actually differ between treatment groups in Study 107.

The following table breaks down severe hypoglycemic event data by which criterion was met, for the overall controlled Phase 2/3 adult Type 1 patient population. This table uses the overall safety review definition of hypoglycemia.

Table 7.1.3.3.1.1.3 Breakdown of Severe Hypoglycemic Event Data for Type 1 Adult Patients by Which Criterion for Severe Hypoglycemia was Met				
	Inhaled Insulin Groups		**SQ Groups**	
Definition of Hypoglycemic Event	**n (total # events = 5134)**	**% of Events Meeting this Criterion**	**n (total # events = 5515)**	**% of Events Meeting this Criterion**
Blood glucose ≤ 36 mg/dL	4836	94.2	5185	94.0
Required assistance	206	4.0	192	3.5
Blood glucose ≤ 36 mg/dL and required assistance	92	1.8	138	2.5
Source: Applicant's Table 2.5.15, Section 2.7.3, pg 261 Includes Studies 102, 106, 107, 1022, 1026, 1027				

For the overall controlled Phase 2/3 Type 1 adult patient population, there was little difference between groups for the percentage of patients who met one or the other criterion for severe hypoglycemia.

The frequency distribution of severe hypoglycemic events (overall safety review definition) among adult Type 1 diabetics was also similar between groups overall. Because there was some variability among trials for the frequency distributions, each trial's data are listed separately.

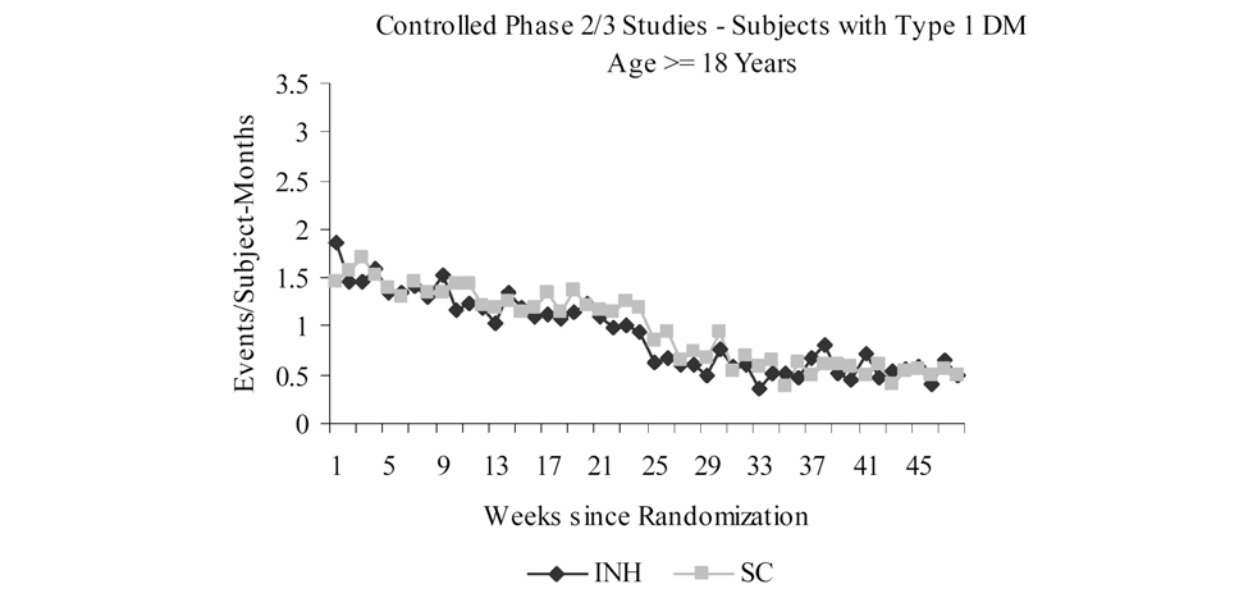
Table 7.1.3.3.1.1.4 Frequency Distribution of Severe[1] Hypoglycemic Events Per Patient, Adult Type 1 Patients							
			% of Patients with Specified Number of Events				
Study	**n**	**Range of Number of Severe Hypoglycemic Events**	**0**	**≤ 5**	**≤ 10**	**≤ 20**	**≤ 30**
All adult Type 1 patients							
Overall Inh ins	691	0-75	20.8	59.8	76.8	90.5	95.9
Overall SQ	686	0-78	22.3	60.4	74.1	87.5	93.9
Study 102							

Table 7.1.3.3.1.1.4 Frequency Distribution of Severe[1] Hypoglycemic Events Per Patient, Adult Type 1 Patients							
			% of Patients with Specified Number of Events				
Study	**n**	**Range of Number of Severe Hypoglycemic Events**	**0**	**≤ 5**	**≤ 10**	**≤ 20**	**≤ 30**
Inh ins	35	0-11	68.6	97.2	97.2	100.0	100.0
SQ	36	0-17	69.4	94.5	94.5	100.0	100.0
Study 106							
Inh ins	136	0-69	13.2	49.3	68.4	85.3	91.8
SQ	132	0-53	12.1	47.6	68.7	83.9	92.3
Study 107							
Inh ins	103	0-49	11.7	45.7	67.0	87.4	95.1
SQ	103	0-78	8.7	39.8	55.4	77.7	88.4
Study 1022IA							
Inh ins	288	0-75	18.8	58.0	76.8	89.6	95.7
SQ	286	0-69	18.9	61.5	73.6	87.0	94.1
Study 1026							
Inh ins	23	0-37	13.0	34.6	56.2	86.5	95.1
SQ	21	0-51	14.3	47.7	62.0	85.9	90.7
Study 1027							
Inh ins	106	0-17	31.1	84.8	94.3	100.0	100.0
SQ	108	0-32	4206	83.3	94.5	98.2	99.1
1 Defined as blood glucose ≤ 36 mg/dL, or requiring assistance **Source: Applicant's Table 18, Section 2.7.3.3.2.1.6, pg 36**							

The number of patients who had either high numbers of severe hypoglycemic events or low numbers of severe hypoglycemic events did not differ between groups.

In both the inhaled insulin and SQ groups, overall hypoglycemia event rates declined over time, with similar rates of decline between groups. This could indicate an initial period of adjustment to the study regimen, with declining incidence of hypoglycemic events as the study progressed, or a decline in reporting of clinical events. Although there was an apparent decline over time in controlled Phase 2/3 studies, severe hypoglycemic adverse events continued to occur in extension studies; please see the serious hypoglycemic adverse event summaries in Appendix 10.5. The occurrence of severe hypoglycemic adverse events cannot be entirely attributed to an initial learning period for inhaled insulin.

Figure 7.1.3.3.1.1.1 Hypoglycemia[1] Event Rates over Time, Adult Type 1 Subjects



Source: Applicant's Figure 2, Section 2.7.3.3.2.1.6, pg 38

1 Defined as BG ≤ 36 mg/dL, or pt required assistance

The applicant summarized time of onset of hypoglycemia events by hour of the day (e.g. 1-2 am, 5-6 pm). Because blood glucose measurements were done before meals (ac) and at bedtime (hs), one would expect higher numbers of events at these times. Inhaled insulin group patients tended to have higher hypoglycemic event rates than SQ group patients in the early morning, while the converse was true for midday. This pattern was true for the overall pattern in Phase 2 and Phase 3 trials, and held true across most studies, as illustrated in the following figures:

Figure 7.1.3.3.1.1.2 Hypoglycemic Event[1] Rates, Onset by Time of Day, Adult Type 1 Patients, Phase 2 and Phase 3 Studies

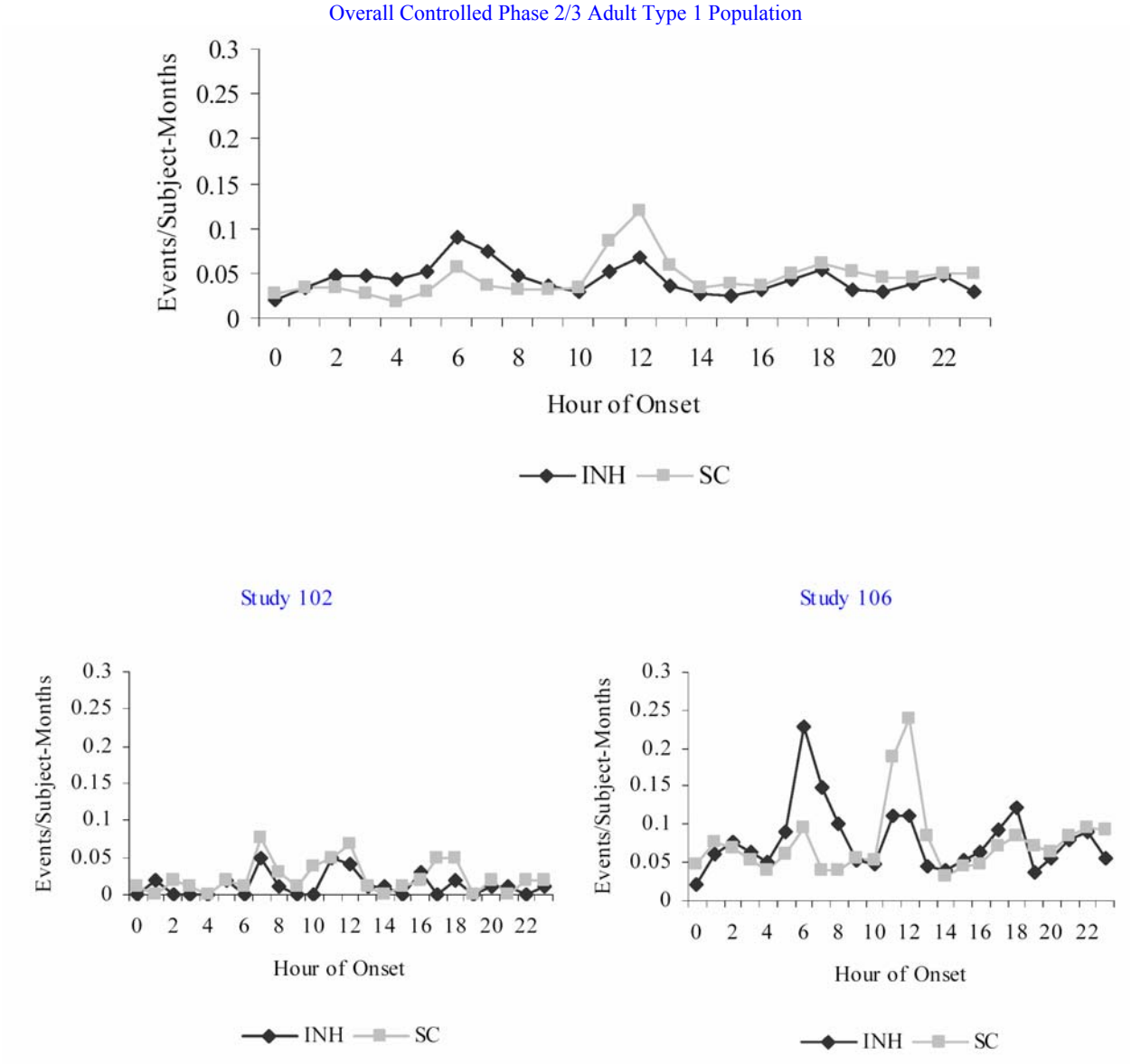
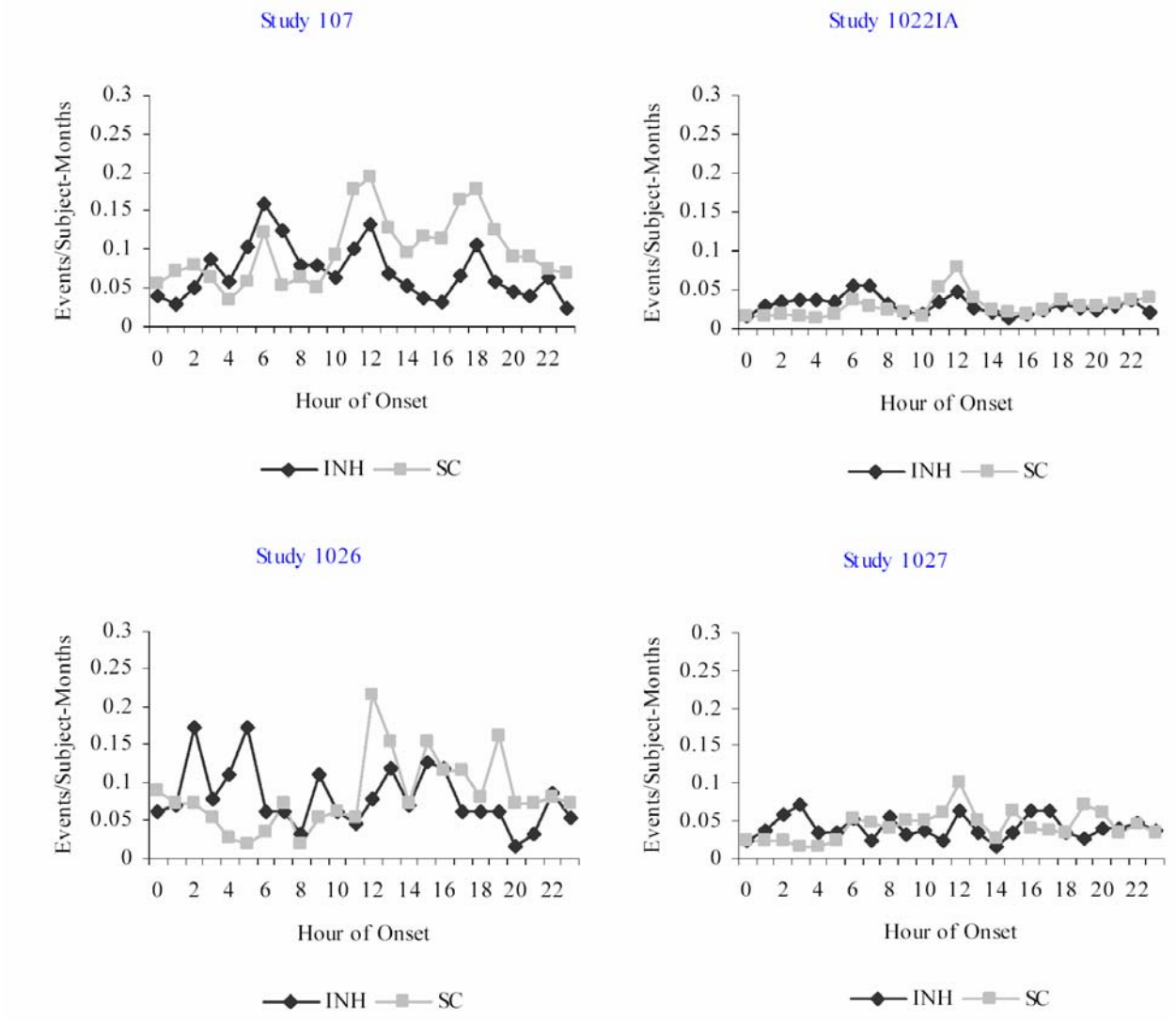


Figure 7.1.3.3.1.1.2 (cont.)



Source: Applicant's Figure 10, pg 82, Efficacy Summary
1 Defined as BG ≤ 36 mg/dL, or pt required assistance

The reason for this consistent pattern of prebreakfast hypoglycemia in inhaled insulin group patients is unclear. One would expect prebreakfast hypoglycemia to be related to evening dosing of longacting insulin, rather than to the patient's short-acting insulin. However, in Study 107, the intensive control study in Type 1 diabetics, mean dose of longacting insulin was actually somewhat lower for inhaled insulin group patients, both for the evening dose and for the total daily dose. Study 1026 was the only study in which 0200 blood sugars were routinely measured (email from Mr Brian Green of Pfizer, 16 Jun 05). In this study, hypoglycemia was more common at 0200 for inhaled insulin group patients than for SQ patients. This could be an inhaled insulin effect for those patients who received inhaled insulin with a bedtime snack, or a peaking effect of an evening longacting insulin. For the overall population of Type 1 diabetics in all Phase 2/3 studies, the majority of hypoglycemic episodes reported as serious adverse events

among inhaled insulin patients occurred in the early morning hours (for those patients for whom serious adverse event narratives were provided; see Table 8.1.3).

In summary, rates of serious hypoglycemic events did not differ between inhaled insulin and SQ insulin groups for the controlled Phase 2/3 adult Type 1 diabetic population. However, in Study 107, the intensive control study, inhaled insulin group patients were more likely (by the applicant's analysis) to have protocol-defined severe hypoglycemia than were SQ group patients. The FDA Biostatistics reviewer questions the applicant's model used in this analysis, however, and it is possible that no difference existed between groups. In the overall controlled Phase 2/3 adult Type 1 population, hypoglycemia was more likely to occur prebreakfast for inhaled insulin patients than for SQ patients; the converse was true for prelunch hypoglycemia, which was more likely to occur in SQ patients. In Study 1026, the only study with routine measurement of 0200 blood sugars, hypoglycemia at 0200 was more likely to occur among inhaled insulin group patients than among SQ group patients. Hypoglycemia reported as a serious adverse event (for inhaled insulin patients) was more likely to occur in the early morning hours than at other times of the day.

7.1.3.3.1.2 Specifically-defined Hypoglycemic Events Among Adult Type 2 Patients

Severe hypoglycemic events were less common among patients with Type 2 diabetes compared to patients with Type 1 diabetes. The same overall safety criteria for severe hypoglycemic events were used, namely a blood glucose of ≤ 36 mg/dL or an event requiring assistance. As with Type 1 diabetes, the majority of hypoglycemic events met the former criterion. However, comparator patients who were not using insulin at baseline (Studies 104, 109, 110, 1001, 1002) were less likely to meet the blood glucose criterion than comparator patients who were using insulin at baseline (Studies 103, 108, 1029) (93% vs 69%).

The following table presents data for severe hypoglycemic (overall safety definition) event rates for adult Type 2 patients. Because several different comparators were used, individual study data for event rates are also presented.

Table 7.1.3.3.1.2.1 Severe Hypoglycemic Events (Defined as Blood Glucose ≤ 36 mg/dL, or Patient Requiring Assistance), Adult Type 2 Patients, Full ITT Population[1]

Study	Treatment Group	Total # Patients in Treatment Group	N (% with Severe Hypoglycemic Event)	Total Events	Total Subject-months	Events per Subject-month	Risk Ratio (95% CI)
All Patients who Were Using Insulin at Study Entry	**Inh ins**	487	132 (27.1%)	353	4139.0	0.085	0.62 (0.55-0.71)
	SQ	480	123 (25.6)	576	4265.1	0.135	
Study 103[2]	**Inh ins**	28	3 (10.7)	5	76.1	0.066	1.61 (0.38-6.72)
	SQ	27	2 (7.4)	3	76.9	0.039	
Study 108[2]	**Inh ins**	146	34 (23.3)	80	793	0.101	0.80 (0.60-1.07)
	SQ	149	28 (18.8)	104	824	0.126	
Study 1029[2]	**Inh ins**	313	95 (30.4)	268	3569.9	0.082	0.58 (0.50-0.67)
	SQ	304	93 (30.6)	469	3364.2	0.139	

Table 7.1.3.3.1.2.1 Severe Hypoglycemic Events (Defined as Blood Glucose ≤ 36 mg/dL, or Patient Requiring Assistance), Adult Type 2 Patients, Full ITT Population[1]

Study	Treatment Group	Total # Patients in Treatment Group	N (% with Severe Hypoglycemic Event)	Total Events	Total Subject-months	Events per Subject-month	Risk Ratio (95% CI)
All Patients who Were not Using Insulin at Study Entry	Inh ins	757	77 (10.2)	135	3320.1	0.041	3.48 (2.37-5.12)
	Comparator	617	19 (3.1)	32	2803.8	0.011	
Study 104[3]	Inh ins	32	2 (6.3)	2	88.5	0.023	NE[4]
	OA[5]	36	0	0	99.4	0	
Study 109[3]	Inh ins	102	17 (16.7)	23	283.3	0.081	NE
	Inh ins + OA	100	21 (21.0)	48	284.3	0.169	
	OA	96	0	0	266.3	0	
Study 110[3]	Inh ins	75	9 (12.0)	15	214.6	0.07	NE
	Rosi[6]	67	0	0	186.9	0	
Study 1001-L[7]	Inh ins + SU	101	4 (4.0)	6	555.5	0.011	1.83 (0.46-7.32)
	Met[8] + SU	93	1 (1.1)	3	505.6	0.006	
Study 1001-H[7]	Inh ins + SU	113	11 (9.7)	14	630.7	0.022	2.09 (0.80-5.44)
	Met + SU	103	6 (5.8)	6	554.5	0.011	
Study 1002-L[7]	Inh ins + Met	125	7 (5.6)	16	683.7	0.023	1.01 (0.50-2.05)
	Gli[9] + Met	119	9 (7.6)	15	634	0.024	
Study 1002-H[7]	Inh ins + Met	109	6 (5.5)	11	579.7	0.019	1.33 (0.53-3.30)
	Gli + Met	103	3 (2.9)	8	557.3	0.014	

1 Includes Studies 103, 104, 108, 109, 110, 1001, 1002, 1029
2 Patients were insulin-using at Study Entry
3 Patients were not using insulin at Study Entry
4 Not estimable
5 Oral agent
6 Rosiglitazone
7 In Studies 1001 and 1002, patients were stratified on the basis of baseline HbA1c; L = 8-9.5; H = 9.5-12. Data are for first 6 months of study for both studies.
8 Metformin
9 Glibenclamide
Source: Applicant's Table 27, Section 2.7.3.3.3.1.6, pg 53

Inhaled insulin group patients were not more likely to experience severe hypoglycemic events than SQ group patients, in studies of Type 2 patients who were using insulin at baseline. However, inhaled insulin group patients were more likely to experience severe hypoglycemia than were patients in oral agent comparator groups in studies of patients who were not insulin-using at baseline. However, control of glycemia was in general better with inhaled insulin than with oral agents, and thus a higher rate of hypoglycemia would be expected. In Studies 104, 109 and 110, all severe hypoglycemic events occurred in inhaled insulin group patients.

As with Type 1 diabetes, the vast majority of severe hypoglycemic events among Type 2 diabetics met the criterion of blood glucose ≤ 36 mg/dL, with relatively few patients requiring assistance during a hypoglycemic episode. There was little difference between treatment groups.

Table 7.1.3.3.1.2.2 Breakdown of Severe Hypoglycemic Event Data for Type 2 Diabetic Patients by Which Criterion for Severe Hypoglycemia was Met

	Inh Ins		SQ	
Definition of Hypoglycemic Event	**n (total # events = 353)**	**% of Events Meeting this Criterion**	**n (total # events = 576)**	
Blood glucose ≤ 36 mg/dL	322	91.2	534	92.7
Required assistance	22	6.2	25	4.3
Glucose ≤ 36 mg/dL and required assistance	9	2.5	17	3.0

Source: Applicant's Table 2.5.16, Section 2.7.1
Includes Studies 103, 108 and 1029

Table 7.1.3.3.1.2.3 Frequency Distribution of Severe[1] Hypoglycemic Events per Patient, Type 2 Patients

				% of Patients with Specified Number of Events			
Study	**Treatment Group**	**Total # Patients in Treatment Group**	**Range of Number of Severe Hypoglycemic Events**	**0**	**≤5**	**≤10**	**≤20**
All Patients who Were Using Insulin at Study Entry	**Inh ins**	487	0-17	72.9	96.2	99.0	99.8
	SQ	480	0-47	74.4	93.8	96.2	99.4
Study 103[2]	**Inh ins**	28	0-3	89.3	100.0	n/a	n/a
	SQ	27	0-2	92.6	100.0	n/a	n/a
Study 108[2]	**Inh ins**	146	0-10	76.7	97.3	100.0	n/a
	SQ	149	0-15	81.2	96.1	97.5	100.0
Study 1029[2]	**Inh ins**	313	0-17	69.6	95.5	98.6	100.0
	SQ	304	0-47	69.4	91.9	95.2	99.3
All Patients who Were not Using Insulin at Study Entry	**Inh ins**	757	0-15	89.8	99.6	99.7	100.0
	Comparator	617	0-6	96.9	99.8	100.0	n/a
Study 104[3]	**Inh ins**	32	0-1	93.8	100.0	n/a	n/a
	OA[5]	36	0	100.0	n/a	n/a	n/a
Study 109[3]	**Inh ins**	102	0-3	83.3	100.0	n/a	n/a
	Inh ins + OA	100	0-15	79.0	98.0	99.0	100.0
	OA	96	0	100.0	n/a	n/a	n/a
Study 110[3]	**Inh ins**	75	0-3	88.0	100.0	n/a	n/a
	Rosi[6]	67	0	100.0	n/a	n/a	n/a
Study 1001-L[7]	**Inh ins + SU**	101	0-3	96.0	100.0	n/a	n/a
	Met[8] + SU	93	0-3	98.9	100.0	n/a	n/a
Study 1001-H[7]	**Inh ins + SU**	113	0-3	90.3	100.0	n/a	n/a
	Met + SU	103	0-1	94.2	100.0	n/a	n/a
Study 1002-L[7]	**Inh ins + Met**	125	0-5	94.4	100.0	n/a	n/a
	Gli[9] + Met	119	0-3	92.4	100.0	n/a	n/a
Study 1002-H[7]	**Inh ins + Met**	109	0-4	94.5	100.0	n/a	n/a
	Gli + Met	103	0-6	97.1	99.0	100.0	n/a

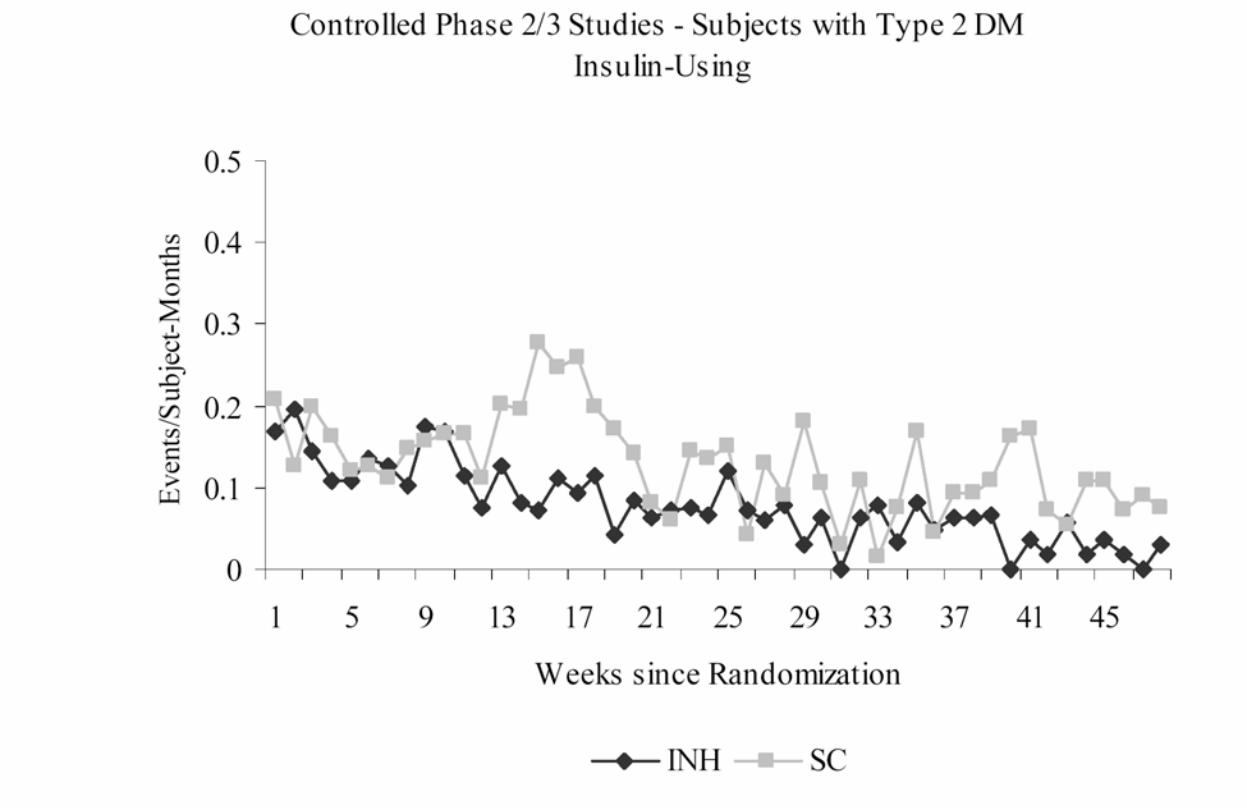
1 Severe hypoglycemia defined as BG ≤ 36 mg/dL, or pt required assistance

For studies in which SQ insulin was the comparator, there was little difference between inhaled insulin and SQ groups for the numbers of patients who had higher numbers of hypoglycemic events; the vast majority of patients had 5 or fewer events. For oral agent comparator studies, one oral agent patient had 6 events, and all other oral agent patients had fewer events. Even among inhaled insulin patients, only a small percentage of patients had >5 events; one patient in

Study 109 had a total of 15 hypoglycemic events; that patient was in the combined inhaled insulin + sulfonylurea group.

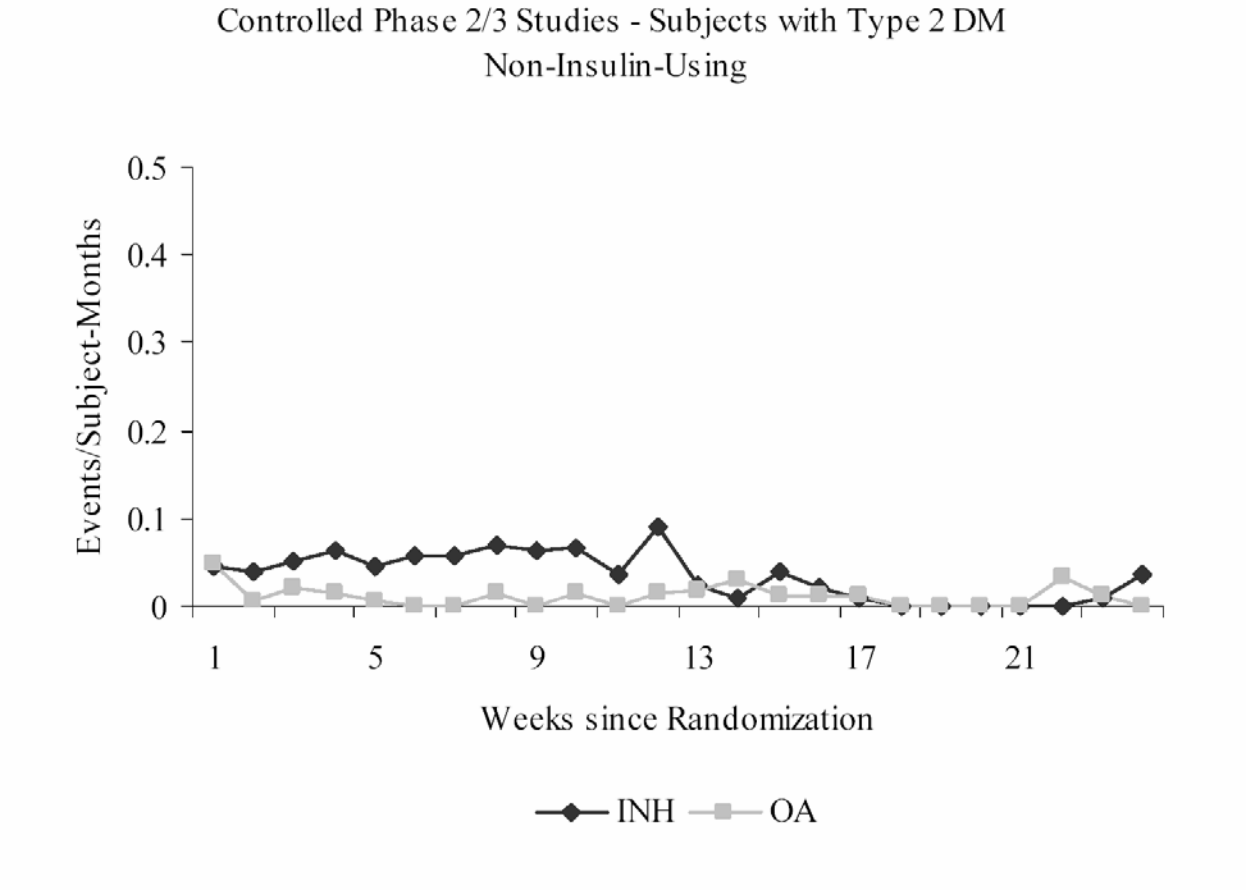
In studies of Type 2 diabetics where SQ was used as a comparator, rates of hypoglycemia declined over time for both SQ and inhaled insulin patients. In studies of Type 2 diabetics where oral agents were used as a comparator, event rates were too low to distinguish a time trend.

Figure 7.1.3.3.1.2.1 Hypoglycemic Events[1] in Type 2 Patients, over Time Since Randomization, Comparator = SQ Insulin



Source: Applicant's Figure 5, ISE
1 Defined as BG ≤ 36 mg/dL, or pt required assistance

Figure 7.1.3.3.1.2.2 Hypoglycemic Events[1] in Type 2 Patients, over Time Since Randomization, Comparator = Oral Agent(s)



Source: Applicant's Figure 5, ISE
1 Defined as BG ≤ 36 mg/dL, or pt required assistance

The applicant provided data regarding time of day of hypoglycemic events, but the number of events was too low to discern a trend for any particular time of day.

Overall, patients with Type 2 diabetes who were insulin using at study entry showed no differences in severe hypoglycemia rates when comparing inhaled insulin to SQ. In trials in which oral agents were the comparators, inhaled insulin patients were more likely to experience hypoglycemia. However, inhaled insulin patients in these oral agent comparator studies also tended to achieve better glycemic control, which carries with it a price of increased hypoglycemic events.

7.1.3.3.1.3 Specifically-defined Hypoglycemia in Pediatric Patients

On 26 May 04, the applicant provided information to DMEDP regarding their pediatric clinical development program. Included in that submission (IND 43313-0263) was some information regarding hypoglycemia in children.

In Studies 106 and 1009, children and adolescents who were treated with inhaled insulin were somewhat less likely to experience protocol-defined hypoglycemia (severe or nonsevere) than patients who were taking SQ insulin. In Study 107, there was no demonstrated difference between groups.

Table 7.1.3.3.1.3.1 Total Protocol-defined Hypoglycemic Event Rates among Pediatric Type 1 Diabetics in Controlled Phase 2/3 Studies

Study	Tx Grp	N	n (%) with Event	Total Events	Total Patient-months	Event Rate (Events/ Pt-Mo)	Risk Ratio (95% CI)
106	Inh Ins	32	32 (100.0)	1427	181.9	7.8	0.89 (0.83, 0.96)
	SQ	29	29 (100.0)	1426	162.5	8.8	
107	Inh Ins	59	59 (100.0)	3063	335.4	9.1	1.04 (0.99, 1.10)
	SQ	59	58 (98.3)	2923	333.4	8.8	
1009	Inh Ins	60	60 (100.0)	1407	175.9	8.0	0.88 (0.82, 0.95)
	SQ	59	58 (98.3)	1548	170.7	9.1	

Source: Applicant's IND 43313, Submission 0263, Table A10

Protocol-defined severe hypoglycemic events did not occur more frequently among pediatric inhaled insulin patients in Studies 106 and 1009. In Study 107, there were 16 events of severe hypoglycemia in the inhaled insulin group, and 10 events in the SQ group. Although the risk ratio was 1.62 for occurrence of severe hypoglycemia for inhaled insulin-treated adolescents vs SQ-treated adolescents, the limits of the confidence interval fell on either side of 1, and therefore the difference between groups was not statistically significant.

Table 7.1.3.3.1.3.2 Severe[1] Protocol-defined Hypoglycemic Event Rates among Pediatric Type 1 Diabetics in Controlled Phase 2/3 Studies

Study	Tx Grp	N	n (%) with Event	Total Events	Total Patient-months	Event Rate (Events/ Pt-Mo)	Risk Ratio (95% CI)
106	Inh Ins	32	7 (21.9)	9	181.9	4.9	0.80 (0.33, 1.98)
	SQ	29	4 (13.8)	10	162.5	6.2	
107	Inh Ins	59	8 (13.6)	16	335.4	4.8	1.62 (0.73, 3.56)
	SQ	59	9 (15.3)	10	333.4	3.0	
1009	Inh Ins	60	9 (15.0)	15	175.9	8.5	0.81 (0.41, 1.61)
	SQ	59	9 (15.3)	18	170.7	10.5	

1 In order to be classified as severe in these studies, patient had the meet all three of the following criteria:

- **patient unable to treat themselves**
- **patient exhibited at least one of the following- memory loss, confusion, uncontrollable behavior, irrational behavior, unusual difficulty in awakening, suspected seizure, seizure, loss of consciousness**
- **measured BG ≤ 49 mg/dL; or if no BG measured, clinical manifestations reversed by oral carbohydrates, subcutaneous glucagon, or intravenous glucose**

Source: Applicant's IND 43313, Submission 0263, Table A11

The table below categorizes hypoglycemic events by other definitions.

Table 7.1.3.3.1.3.3 Hypoglycemic Event Rates Categorized by Definition of Hypoglycemia, Pediatric Type 1 Diabetics, Controlled Phase 2/3 Studies

Study	Tx Grp	N	Total Events	Sx of Hypogly, No BG n (%)	Sx of Hypogly, BG ≤ 59 mg/dL n (%)	No Sx of Hypogly, BG ≤49 mg/dL n (%)	BG ≤ 36 mg/dL or Required Assistance n (%)
106	Inh Ins	32	1427	71 (5.0)	1232 (86.3)	124 (8.7)	221 (15.5)
	SQ	29	1426	29 (2.0)	1193 (83.7)	203 (14.2)	242 (17.0)
107	Inh Ins	59	3063	34 (1.1)	2502 (81.7)	522 (17.0)	543 (17.7)

Table 7.1.3.3.1.3.3 Hypoglycemic Event Rates Categorized by Definition of Hypoglycemia, Pediatric Type 1 Diabetics, Controlled Phase 2/3 Studies

Study	Tx Grp	N	Total Events	Sx of Hypogly, No BG n (%)	Sx of Hypogly, BG ≤ 59 mg/dL n (%)	No Sx of Hypogly, BG ≤49 mg/dL n (%)	BG ≤ 36 mg/dL or Required Assistance n (%)
	SQ	59	2923	31 (1.1)	2483 (84.9)	409 (14.0)	528 (18.1)
1009	Inh Ins	60	1407	23 (1.6)	1047 (74.4)	337 (24.0)	240 (17.1)
	SQ	59	1548	26 (1.6)	1176 (76.0)	346 (22.4)	200 (12.9)

Source: Applicant's IND submission 43313-0263, Table A13
Sum of percentages in some groups may exceed 100% because some patients met multiple criteria.

For most categories, rates in the inhaled insulin group did not exceed rates in the SQ group. In Study 1009, more patients in the inhaled insulin group had hypoglycemic events characterized by a blood sugar ≤ 36 mg/dL or a requirement for the assistance of another person than did patients in the SQ group.

Overall, protocol-defined hypoglycemia, and protocol-defined severe hypoglycemia did not occur statistically significantly more frequently in pediatric patients treated with inhaled insulin compared to those treated with SQ alone.

7.1.3.3.2 Development of Insulin Antibodies

Across the development program, greater increases occurred in insulin antibody levels for patients taking inhaled insulin than for patients taking either subcutaneous insulin alone or oral agents alone. This observation led to concerns about potential clinical consequences of this antibody formation. The clinical review of insulin antibody data attempted to answer several questions:

- What were the rates of insulin antibody seroconversion among study populations?
- How did insulin antibody levels compare among different populations, and how did these levels correlate with demographic data?
- Did the qualitative nature of insulin antibodies differ between treatment groups?
- Did patients who increased their insulin antibody levels have more adverse events of any given kind?
- Specifically, did such patients have more pulmonary, allergic, or other immunologic events?
- Was there evidence that these antibodies could neutralize the action of insulin?
- Was there evidence that these antibodies could have other effects on insulin pharmacodynamics or overall glycemic control?
- What happened to insulin antibody levels after discontinuation of inhaled insulin?

7.1.3.3.2.1 What were the rates of insulin antibody seroconversion among study populations?

Two different types of insulin antibody measurement methods were used. In earlier studies (106, 107, 108, 109, 110, 111, 1009, 1036), a semi-quantitative radioligand binding assay was used (Mayo Medical Laboratories, Rochester, MN). In this assay, results were expressed as "% binding", and the lower limit of quantitation was 3% binding. Because the Mayo assay was not useful for quantifying the highest levels of antibodies, a quantitative radioligand binding assay was developed and validated by Esoterix®, Inc (Calabasas Hills, CA; Moxness M 2002). In this assay, results were expressed as µU/mL, with a lower limit of quantitation of 2.1 µU /mL. This assay was used in Studies 1001, 1002, 1022, 1026, 1027 and 1029.

In studies in which the Esoterix® assay was used, 75% (608/811) of all inhaled insulin patients (combined Type 1 and Type 2) who had an undetectable level of insulin antibodies at beginning of study had measurable insulin antibodies at end of study (or last insulin antibody measurement). This compares to a 9.9% (77/778) seroconversion rate among comparator patients. The following tables illustrate seroconversion rates in Type 1 adults, Type 1 children, and Type 2 adults. Because of the differences in assays, separate tables are provided by assay type for each patient category.

Table 7.1.3.3.2.1.1. Seroconversion[1] Rates Among Type 1 Diabetics in Studies[3] Using Semiquantitative Mayo Assay

	Inhaled Insulin # Pts Converting (% Pts Converting)[2]	SQ # Pts Converting (% Pts Converting)[2]
Study 106, all ages	70 (87.5)	15 (20.5)
Study 107, all ages	73 (89.0)	9 (12.3)
Study 1009, all ages	10 (90.9)	4 (36.4)
Combined Studies, pts age ≥ 18 yrs	118 (86.8)	20 (17.4)
Combined Studies, pts age <18 yrs	35 (94.6)	8 (19.0)
Combined Studies, pts age 12-18 yrs	25 (96.2)	4 (13.3)
Combined Studies, all ages	153 (88.4)	28 (17.8)

1 Seroconversion defined as having nonmeasurable insulin antibodies at baseline and measurable insulin antibodies at end of study
2 % of patients who had nonmeasurable antibodies at baseline who then seroconverted to measurable insulin antibodies at end of study
3 6 mo data for Studies 106 and 107; 3 mo data for Study 1009
Source: Applicant's Table 1.1.1, submission N-000-BZ, 6 May 05

Table 7.1.3.3.2.1.2 Seroconversion[1] Rates Among Type 1 Adult[3] Diabetics in Studies Using Quantitative Esoterix® Assay

	Inhaled Insulin # Pts Converting (% Pts Converting)[2]	SQ # Pts Converting (% Pts Converting)[2]
Study 1022	111 (91.7)	29 (25.0)
Study 1026	11 (91.7)	6 (35.3)
Study 1027	39 (78.0)	8 (15.7)
Combined Studies	161 (88.0)	43 (23.4)

1 Seroconversion defined as having nonmeasurable insulin antibodies at baseline and measurable insulin antibodies at end of study
2 % of patients who had nonmeasurable antibodies at baseline who then seroconverted to measurable insulin antibodies at end of study
3 Studies 1022, 1026 and 1027 included only adult patients. 2 yr data for Study 1022, 6 mo data for Study 1026, 3 mo data for Study 1027
Source: Applicant's Table 1.2.1, Submission N-000-BZ, 6 May 05

Among Type 1 diabetics, rates of seroconversion were significantly higher among patients in inhaled insulin groups than among those in SQ only groups. Rates of seroconversion were higher among pediatric patients than among adult patients.

Table 7.1.3.3.2.1.3 Seroconversion[1] Rates Among Type 2 Adult[3] Diabetics in Studies Using Semiquantitative Mayo Assay

	Inhaled Insulin # Pts Converting (% Pts Converting)[2]	Comparator # Pts Converting (% Pts Converting)[2]
Study 104	5 (17.9)	no data
Study 108	65 (56.0)	8 (7.2)
Study 109	83 (43.5)	no data
Study 110	28 (41.8)	no data
Type 2 non-insulin-using at baseline	116 (40.6)	no data
Combined Studies, all Type 2s	181 (45.0)	not calculable

1 Seroconversion defined as having nonmeasurable insulin antibodies at baseline and measurable insulin antibodies at end of study
2 % of patients who had nonmeasurable antibodies at baseline who then seroconverted to measurable insulin antibodies at end of study
3 All Type 2 studies involved adults only. 3 mo data for Studies 104, 109, and 110; 6 mo data for Study 108
Source: Applicant's Table 1.1.1, submission N-000-BZ, 6 May 05

Table 7.1.3.3.2.1.4 Seroconversion[1] Rates Among Type 2 Adult[3] Diabetics in Studies Using Quantitative Esoterix® Assay

	Inhaled Insulin # Pts Converting (% Pts Converting)[2]	Comparator # Pts Converting (% Pts Converting)[2]
Study 1001	158 (74.9)	29 (25.0)
Study 1002	141 (65.0)	2 (1.0)
Study 1029	148 (74.0)	31 (14.9)
Type 2 non-insulin-using at baseline	299 (69.9)	3 (0.8)
Combined Studies, all Type 2s	447 (71.2)	34 (5.7)

1 Seroconversion defined as having nonmeasurable insulin antibodies at baseline and measurable insulin antibodies at end of study
2 % of patients who had nonmeasurable antibodies at baseline who then seroconverted to measurable insulin antibodies at end of study
3 All Type 2 studies involved adults only. 2 yr data for Studies 1001 and 1002; 1 yr data for Study 1029
Source: Applicant's Table 1.2.1, Submission N-000-BZ, 6 May 05

Seroconversion rates were significantly higher among Type 2 patients in inhaled insulin groups than among Type 2 patients in comparator groups. Seroconversion rates were lower among Type 2 patients than among Type 1 patients.

7.1.3.3.2.2 How did insulin antibody levels compare among different populations, and how did these levels correlate with demographic data?

For Type 1 diabetic patients, inhaled insulin was associated with higher end-of-study insulin antibody levels, and with greater change from baseline in insulin antibody levels, than was SQ insulin.

The following tables illustrate the differences in antibody levels for Type 1 adult patients.

Table 7.1.3.3.2.2.1 Mean and Median Insulin Antibody Levels at Baseline and End of Study, Adult Type 1 Patients, Studies 106 and 107, Mayo Assay (Semiquantitative, Expressed as % Binding[2])

	Inh Ins			SQ		
	n[1]	Mean (SD)	Median	n	Mean (SD)	Median
Baseline	215	5.7 (9.8)	1.5	203	6.1 (10.3)	1.5
End of Study (6 months)	215	27.7 (20.7)	25.0	203	7.1(11.8)	1.5
Change from Baseline	215	22.0 (17.9)	20.5	203	1.0 (5.3)	0.0

1 n = number of patients evaluated for antibody levels at each time point

Table 7.1.3.3.2.2.1 Mean and Median Insulin Antibody Levels at Baseline and End of Study, Adult Type 1 Patients, Studies 106 and 107, Mayo Assay (Semiquantitative, Expressed as % Binding[2])

	Inh Ins			SQ		
	n[1]	Mean (SD)	Median	n	Mean (SD)	Median

2 Applicant imputed values at lower limit of binding (3%) as 1.5%
Source: Applicant's Tables 3, 1.1.1, 1.1.4.1, and 1.1.4.2, Section 5.3.5.3.2

Table 7.1.3.3.2.2.2 Mean and Median Insulin Antibody Levels at Baseline and End of Study, Adult Type 1 Patients, Studies 1022, 1026 and 1027, Esoterix® Assay (Quantitative, Expressed as µU /mL[2])

	Inh Ins			SQ		
	n[1]	Mean (SD)	Median	n	Mean (SD)	Median
Baseline	415	28.3 (187.7)	3.6	420	20.9 (80.5)	3.5
3 Months	393	121.7 (300.1)	31.0	397	21.3 (71.6)	3.6
Change from Baseline to 3 Months	386	102.1 (285.4)	25.0	389	-0.19 (28.7)	0.0
6 Months	283	179.9 (239.1)	83.0	290	24.5 (91.9)	4.4
Change from Baseline to 6 Months	278	160.6 (224.3)	72.5	286	1.18 (20.78)	0.0

1 n = number of patients evaluated for antibody levels at each time point
2 Applicant imputed values at the lower limit of quantitation (2.1 µU /mL) as 1.05 µU /mL
Source: Applicant's Tables 3, 1.1.1, 1.1.4.1, and 1.1.4.2, Section 5.3.5.3.2

End-of-study and change from baseline in insulin antibody levels were higher for pediatric patients than for patients ages 18 or older, as illustrated in the following table. For those patients ages 18 and over taking inhaled insulin, there was little difference between adult age groups for mean antibody levels at end-of-study, and little difference between adult age groups for change in antibody levels from baseline.

Table 7.1.3.3.2.2.3 Age Differences for End-of-Study Insulin Antibody Levels and Change from Baseline in Insulin Antibody Levels, Type 1 Patients, Controlled Phase 3 Studies which Included Children[2] (Mayo Assay, % Binding)

Age Range	Measurement	Inh Ins		SQ	
		n	% Binding[1] Mean (SD)	n	% Binding Mean (SD)
< 18 yrs	Baseline	138	10.37 (11.60)	138	8.71 (9.34)
	End-of-Study	138	36.12 (19.00)	138	10.08 (11.29)
	Change from Baseline	138	25.76 (15.89)	138	1.37 (4.53)
18-44 yrs	Baseline	155	5.15 (8.93)	149	5.73 (10.85)
	End-of-Study	155	26.92 (20.72)	149	7.10 (12.69)
	Change from Baseline	155	21.77 (18.11)	149	1.37 (5.12)
45-64 yrs	Baseline	59	7.11 (11.89)	53	6.88 (8.63)
	End-of-Study	59	29.75 (20.94)	53	6.92 (8.87)
	Change from Baseline	59	22.64 (17.47)	53	0.05 (5.66)
65-74 yrs	Baseline	1	5.00 (n/a)	1	13.00 (n/a)
	End-of-Study	1	24.00 (n/a)	1	15.00 (n/a)
	Change from Baseline	1	19.00 (n/a)	1	2.00 (n/a)

1 Applicant imputed values at lower limit of binding (3%) as 1.5%
2 Studies 106, 107, 1009
Source: Applicant's Table 3.1.1, Section 5.3.5.3.2, p 91

Female patients had higher mean end-of-study insulin antibodies, and had greater changes from baseline antibody levels than did male patients, as illustrated in the following tables:

Table 7.1.3.3.2.2.4 Gender Differences in Mean End-of-Study and Change-from-Baseline in Insulin Antibodies, Type 1 Patients, Controlled Phase 3 Studies 106 and 107 (Mayo Assay % Binding)

	Inh Ins		SQ	
	Male (n = 90) Mean[1] % Binding (SD)	Female (n = 44) Mean % Binding (SD)	Male (n = 90) Mean % Binding (SD)	Female (n = 43) Mean % Binding (SD)
Baseline	5.17 (9.39)	6.24 (10.28)	6.96 (12.57)	4.99 (6.48)
End-of-Study (6 months)	23.04 (17.83)	32.64 (22.46)	8.20 (14.27)	5.77 (7.63)
Change from Baseline	17.86 (15.47)	26.40 (19.20)	1.24 (6.49)	0.78 (3.28)

1 Lower limit of quantitation = 3%, imputed by applicant as 1.5%; upper limit of quantitation = 90%, imputed by applicant as 91%
Source: Applicant's Table 3.2.1, Section 5.3.5.3.2

Table 7.1.3.3.2.2.5 Gender Differences in Mean End-of-Study and Change-from-Baseline in Insulin Antibodies, Type 1 Patients, Controlled Phase 3 Study 1022 (Esoterix® Assay, µU /mL)

	Inh Ins		SQ	
	Male (n = 164) Mean[1] (SD)	Female (n = 121) Mean (SD)	Male (n = 158) Mean (SD)	Female (n = 126) Mean (SD)
Baseline	16.14 (39.94)	58.47 (340.47)	16.06 (47.64)	32.45 (127.00)
End-of-Study (12 months)	234.20 (467.59)	434.97 (1194.20)	15.67 (40.51)	38.05 (197.79)
Change from Baseline	218.06 (446.16)	376.50 (910.19)	-0.38 (26.50)	5.60 (82.48)

1 Lower limit of quantitation = <2.1 µU/mL, imputed by applicant as 1.05
Source: Applicant's Table 3.2.4, Section 5.3.5.3.2

The numbers of non-Caucasian Type 1 patients in the controlled studies for which antibody data were available were too small for meaningful comment on differences in antibody changes by race.

Patients with Type 2 diabetes who were exposed to inhaled insulin had higher mean insulin antibody levels at end of study, and greater changes from baseline, than did patients in comparator groups. This difference was more marked among patients who had been using injected insulin prior to study than it was for patients who had not been using injected insulin prior to study.

Table 7.1.3.3.2.2.6 Mean and Median Insulin Antibody Levels at Baseline and End of Study, Type 2 Patients, Controlled Phase 2/3 Studies[3] Using Mayo Assay (Semiquantitative, Expressed as % Binding[2])

	Inh Ins			Comparator		
	n[1]	Mean (SD)	Median	n	Mean (SD)	Median
Insulin-using at Study Entry	134			133		
Baseline		2.7 (4.3)	1.5		4.1 (9.3)	1.5
End of Study (6 months)		12.8 (18.2)	5.0		4.0 (8.0)	1.5
Change from Baseline		10.2 (16.1)	3.5		-0.1 (3.3)	0.0
Non-insulin-using at Study Entry	290			181		
Baseline		1.8 (4.6)	1.5		1.5 (0.3)	1.5
End of Study (6 months)		6.0 (8.0)	1.5		1.5 (0.0)	1.5
Change from Baseline		4.3 (9.2)	0.0		0.0 (0.3)	0.0

1 n = number of patients evaluated for antibody levels at each time point
2 Applicant imputed values at lower limit of binding (3%) as 1.5%
3 Studies 104, 108, 109, 110
Source: Applicant's Table 11, Section 5.3.5.3.2

Table 7.1.3.3.2.2.7 Mean and Median Insulin Antibody Levels at Baseline and End of Study, Type 2 Patients, Controlled Phase 2/3 Studies[3] Using Esoterix® Assay (Quantitative, Expressed as µU/mL[2])

	Inh Ins			Comparator		
	n[1]	Mean (SD)	Median	n	Mean (SD)	Median
Insulin-using at Study Entry						
Baseline	307	12.2 (36.9)	1.1	307	14.9 (86.5)	1.1
End of Study (6 months)	203	78.2 (187.0)	17.0	212	14.6 (102.9)	1.1
Change from Baseline	202	68.5 (178.7)	13.5	208	3.5 (59.7)	0.0
Non-insulin-using at Study Entry						
Baseline	452	1.1 (2.2)	1.0	415	1.0 (0.2)	1.0
End of Study (12 months)	321	16.7 (48.4)	5.4	280	1.0 (0.1)	1.0
Change from Baseline	316	15.6 (48.9)	4.4	276	0.0 (0.2)	0.0

1 n = number of patients evaluated for antibody levels at each time point
2 Applicant imputed values at lower limit of quantitation (2.1 µU/mL) as 1.05
3 Studies 1001, 1002, 1029
Source: Applicant's Table 11, Section 5.3.5.3.2

For Type 2 patients, there was little difference by age in 3-month studies (Studies 104, 109, 110) in mean insulin antibody levels at end of study and in change from baseline in insulin antibody levels. Patients who were age 65 years or older did tend to have higher values in longer studies, and in studies using the Esoterix® assay, mean antibody levels appeared to correlate with age group up to age 74. These changes are illustrated in the following tables.

Table 7.1.3.3.2.2.8 Age Differences in Insulin Antibody Changes at 6 Months of Study, Type 2 Diabetics in Inhaled Insulin Group, Study 108 (Mayo Semiquantitative Assay, % Binding)

	Age 18-44 Yrs n = 10 Mean[1] % Binding (SD)	Age 45-64 Yrs n = 86 Mean % Binding (SD)	Age 65-74 Yrs n = 31 Mean % Binding (SD)	Age ≥ 75 Yrs n = 7 Mean % Binding (SD)
Baseline	2.55 (3.32)	1.99 (2.29)	4.85 (7.66)	1.50 (0.00)
End of Study	9.50 (12.12)	8.98 (13.15)	24.47 (26.72)	13.29 (13.04)
Change from Baseline	6.95 (11.03)	6.98 (11.96)	19.61 (23.47)	11.79 (13.04)

1 Applicant imputed lower limit of quantification (3%) as 1.5%, and upper limit of quantification (90%) as 91%
Source: Applicant's Table 3.1.2, Section 5.3.5.3.2

Table 7.1.3.3.2.2.9 Age Differences in Insulin Antibody Changes at 12 Months of Study, Type 2 Diabetics in Inhaled Insulin Group, Study 1029 (Esoterix® Quantitative Assay, µU/mL)

	Age 18-44 Yrs n = 34 Mean[1] (SD)	Age 45-64 Yrs n = 202 Mean (SD)	Age 65-74 Yrs n = 67 Mean (SD)	Age ≥ 75 Yrs n = 4 Mean (SD)
Baseline	9.81 (23.78)	10.68 (36.11)	18.49 (44.81)	2.80 (2.23)
End of Study	73.10 (140.18)	88.68 (202.15)	114.03 (254.36)	90.48 (141.68)
Change from Baseline	63.29 (126.04)	78.00 (193.88)	95.54 (250.32)	87.68 (141.33)

1 Applicant imputed lower limit of quantification (2.1 µU/mL) as 1.05 µU/mL
Source: Applicant's Table 3.1.5, Section 5.3.5.3.2

Table 7.1.3.3.2.2.10 Age Differences in Insulin Antibody Changes at 24 Months of Study, Type 2 Diabetics in Inhaled Insulin Group, Studies 1001 and 1002 (Esoterix® Quantitative Assay, µU/mL)

	Age 18-44 Yrs n = 35 Mean[1] (SD)	Age 45-64 Yrs n = 293 Mean (SD)	Age 65-74 Yrs n = 92 Mean (SD)	Age ≥ 75 Yrs n = 13 Mean (SD)
Baseline	1.00 (0.00)	1.03 (0.41)	1.56 (4.92)	1.00 (0.00)
End of Study	4.13 (4.87)	12.29 (37.18)	19.45 (50.04)	34.70 (66.86)
Change from Baseline	3.13 (4.87)	11.25 (37.16)	17.89 (50.43)	33.70 (66.86)

1 Applicant imputed lower limit of quantification (2.1 µU/mL) as 1.05 µU/mL
Source: Applicant's Table 3.1.6, Section 5.3.5.3.2

For Type 2 patients, no relationship was demonstrated between gender and insulin antibody changes, and no consistent relationship was demonstrated between race and insulin antibody changes.

7.1.3.3.2.3 Did the qualitative nature of insulin antibodies differ between treatment groups?

Anti-insulin antibodies appeared to be predominantly IgG for both inhaled and SQ patients, and antibodies of other immunoglobulin classes did not appear to occur with detectable frequency. The applicant analyzed residual samples from 88 patients from Studies 107 and 106, and found that serum IgG anti-insulin antibodies predominated in both inhaled and SQ patients, and anti-insulin IgG levels correlated directly with total insulin antibody levels. For both inhaled and SQ group patients, anti-insulin IgA, IgE and IgM levels were below the limit of quantitation.

The applicant also examined the insulin binding capacity profile, using a range of insulin concentrations, for patients in Study 1026 at end of study. For inhaled insulin group patients, the profile was consistent with predominantly low affinity antibodies with high binding capacity.

This insulin binding capacity pattern for the inhaled insulin group is similar to the pattern described in studies for subcutaneous insulin in the medical literature. High affinity antibodies have been associated with clinical concerns more often than low affinity antibodies (the type seen with inhaled insulin), and characteristically slow the early increase in plasma free insulin after subcutaneous insulin injection, with impairment of postprandial glucose control (van Haeften 1987). Low affinity insulin antibodies have been associated in rare circumstances with spontaneous autoimmune hypoglycemia (Basu 2005). Please see the discussion below regarding the evaluation for an association between severe hypoglycemia and insulin antibodies. The clinical reviewer noted that the applicant's figures (Section 5.3.5.3.2, pages 228-231) regarding these insulin binding capacity profiles were inconsistent with the applicant's stated findings. The applicant was notified and intends to submit revised figures and data for further review; these data had not been received as of 5 Jul 05.

7.1.3.3.2.4 Did patients who increased their insulin antibody levels have more adverse events of any given kind? Specifically, did such patients have more pulmonary, allergic, or other immunologic events?

7.1.3.3.2.4.1 Allergic Events

In the overall Phase 2/3 controlled populations, overall events of an allergic nature occurred with similar frequency between inhaled insulin patients and SQ group patients. For Type 1 patients, the event term "allergic reaction" occurred in 31/698 (4.4%) of inhaled insulin patients vs 23/705 (3.3%) of SQ patients, and the term "rhinitis" occurred in 96/698 (13.8%) of inhaled insulin patients vs 67/705 (9.5%) of SQ patients. Narratives were not provided for these patients, and antibody data were not available for analyses for possible relationships. Numerous other event terms were examined with no difference between groups for Type 1 patients. For Type 2 patients, no significant difference was observed between inhaled insulin patients and comparator patients for any given type of allergic adverse event.

Please see Table 7.1.3.3.2.5 below for adverse events occurring among patients who had the highest antibody levels (>2,000 μU/mL by Esoterix® assay). Among Type 1 patients with antibody levels above this range, 3/33 experienced events of a potentially allergic nature (one case each of allergic bronchiolitis, dermatitis of the face and arms, and bilateral eyelid swelling).

7.1.3.3.2.4.2 Hypoglycemia

The applicant addressed the question of hypoglycemia by creating scatter plots in which end-of-study insulin antibodies were plotted against the monthly incidence of hypoglycemic events. The applicant found no association between these variables (applicant's Figures 2.20.1, pgs 233-240, Section 5.3.5.3.2). Separate plots were created for Type 1 and Type 2 patients, and Type 2 patients were evaluated separately by insulin-using status at study entry.

The applicant also addressed the issue of hypoglycemia in relation to antibody binding affinity and capacity by creating scatter plots of the range of affinities from Study 1026 (described

above) against the monthly incidence of hypoglycemic events. However, the figures provided by the applicant to illustrate this point are not consistent with the applicant's stated findings. The applicant was notified of this observation, and plans to submit revised figures and data; these have not been received as of 5 Jul 05.

The following table examines antibody levels among patients who had severe hypoglycemic events, and among those who did not. Severe hypoglycemic events were defined as events requiring the assistance of another person, or events in which the blood glucose was ≤ 36 mg/dL.

Table 7.1.3.3.2.4.2 Mean End-of-Study Antibody Levels for Patients who Did and Did Not have Severe Hypoglycemic Events, Type 1 Patients

	total n	Mean End-of-Study Insulin Antibodies (SD)
Inhaled insulin patients with severe hypoglycemic events	71	255.6 (309.3)
Inhaled insulin patients who did not have severe hypoglycemic events	367	254.3 (777.3)
Inhaled insulin patients overall	438	254.5 (722.4)
SQ patients who had severe hypoglycemic events	92	17.9 (39.7)
SQ patients who did not have severe hypoglycemic events	345	24.1 (126.2)
SQ pts overall	437	22.8 (113.7)

Analysis by Dr. Mele, Biostatistics
Source datasets: insulin antibody datasets, hypoglycemia dataset; includes data from Studies 104, 107-110, 1001, 1002, 1009, 1022, 1026-1030

Although one cannot make strong inferences from an analysis of a subset of an outcome variable, these data do not appear to demonstrate obvious differences in antibody levels for patients who had severe hypoglycemic events.

7.1.3.3.2.5 Characteristics of Patients with Highest Insulin Antibody Levels

The applicant identified all patients in studies using the Esoterix® antibody assay who had insulin antibody levels >2,000 μU /mL. For those studies in which the Mayo assay had been used, the applicant used residual sera when available to re-examine antibody levels using the Esoterix® assay. A total of 37 patients were identified who had insulin antibody levels >2,000 μU/mL. The following table summarizes their characteristics.

Table 7.1.3.3.2.5 Summary Characteristics of Patients with Antibody (Ab) Levels >2,000 µU/mL by Esoterix® Assay

Pt ID	Tx	Age	Sex	DM Type	Pk[3] Ab in µU/mL	Day[1] of Pk Ab	AE	Study Day(s) of AE(s)	Last A1c (%)[2]	Early W/D?	Comment
111-5005-7684	Inh	43	F	1	3,624	719 (1)	Breast lump	170	6.8	yes (Day 720, insuff clin response)	8-10 hypoglycemic events per week at time of study w/d
							Resp infxn	256			
							Cough	571			
							Flu	697			
111-5007-7331	Inh	52	F	1	3,008	389	Cough	58, 515	7.9	no	8 severe hypoglycemic events
							Severe URI	426			
							Expiratory wheezing	522			
							Foot fracture	457			
111-5013-6609	Inh	41	F	1	2,348	711	No resp or allergic AEs; no SAEs	n/a	8.3	no	Screening HbA1c 6.7%
111-5025-6591	Inh	22	F	1	4,895	737	URI	530	7.3	no	
							Flu	919			
111-5030-6883	Inh	53	F	1	2,602	714	Allergic bronchiolitis	502	6.3	no	13 severe hypoglycemic events
							Bibasilar rales	614			
							Right upper lung nodule	628			
							Anterior mediastinal soft tissue density	628			
							Benign granuloma left inferior lung	615			
							Benign granuloma left medial lung	615			
							URI	879			
							Hypoglycemia, LOC, hypothermia	7			
							Hypoglycemia, unconsciousness	111			
							Hypoglycemia, altered LOC	92			
111-5045-1383	Inh	46	M	2	3,416	503 (104)	Severe CHF	503 (97)	9.7	yes (same day as pk Ab; for CHF)	First Ab >2,000 was 2,024 (45 days after inh ins d/c; total days inh ins = 503).
							Decline in DLco	459			
							URI	468			
111-5047-6555	Inh	38	F	1	3,240	741	Decline in DLco	77	7.0		First Ab >2,000 was 2,348 (inh ins day 544)
							URI	598			
							Influenza with hospitalization	654			

Table 7.1.3.3.2.5 Summary Characteristics of Patients with Antibody (Ab) Levels >2,000 µU/mL by Esoterix® Assay

Pt ID	Tx	Age	Sex	DM Type	Pk[3] Ab in µU/mL	Day[1] of Pk Ab	AE	Study Day(s) of AE(s)	Last A1c (%)[2]	Early W/D?	Comment
111-5048-6241	Inh	60	M	1	2,810	700 (27)	Pneumonia	572	7.9		First Ab >2,000 was 2,596 on day 673 of inh ins; two severe hypoglycemic events
							Cough	846			
111-5051-6870	Inh	25	F	1	2,470	375	URI	13	8.2		
							Flu	162			
							Decline in DLco	186			
111-5056-7711	Inh	51	M	1	2,057	946	Decline in DLco	511	9.0		2 severe hypoglycemic episodes
							Dermatitis face and arms	842			
							Cough	44			
							Decreased FEF2575	252			
							Mixed obstructive/ restrictive lung disease	1135			
							URI	536			
							Flu	787			
							Unstable angina	877			
111-5059-6683	Inh	44	M	1	2,184	180	Decline in DLco	382	8.4	yes (Day 382, same day as decline in DLco, reason given = insuff clin response)	
111-5079-3321	Inh	10	F	1	2,937	355	Decline in DLco	172	8.1		
							URI	103			
111-5079-3324	Inh	10	F	1	2,838	624	URI	258, 531, 678	9.9	yes (Day 689- "subject decided not to go into the PFT Trends amendment part of the study")	8 severe hypoglycemic episodes; episode of DKA
111-5079-3402	Inh	10	F	1	3,608	449	URI	23, 100, 132, 335, 456, 555, 567, 601	8.4		
							Expiratory wheezing	337, 566			
							Decreased expiratory reserve volume	337			
							Cough	335			
111-5084-3354	Inh	9	M	1	3,300	664	Productive cough	91	7.7		
							URI	140, 366, 395, 818			
111-5089-7567	Inh	12	F	1	3,248	806	Cough	58	12.2	yes (Day 824, elev HbA1c)	

Table 7.1.3.3.2.5 Summary Characteristics of Patients with Antibody (Ab) Levels >2,000 µU/mL by Esoterix® Assay

Pt ID	Tx	Age	Sex	DM Type	Pk[3] Ab in µU/mL	Day[1] of Pk Ab	AE	Study Day(s) of AE(s)	Last A1c (%)[2]	Early W/D?	Comment
111-5089-7570	Inh	16	F	1	2,426	724	Onset of reactive airway disease	263	10.8		
111-5091-3007	Inh	10	F	1	4,092	371	"Cold symptoms"	383, 477, 513, 553, 605	9.2		
111-5091-3010	Inh	10	F	1	2,140	443	Viral respiratory tract infection	123, 172, 185, 193, 204, 323, 509	8.9		
							Cough	1			
111-5092-3023	Inh	7	F	1	2,101	629	Decline in DLco	86	8.0	yes (Day 671, "frequent visits too difficult to arrange")	
							URI	151, 216, 338, 567			
							Cough	171			
111-5092-3043	Inh	9	F	1	2,272	351	URI	78, 290	6.6		1 severe hypoglycemic event
							Cough	86			
111-5096-6335	Inh	13	M	1	4,972	179	Bilat eyelid swelling	48	8.9	yes (Day 403- "interested in pump")	
							URI	7, 72, 176			
111-5127-7774	Inh	43	F	1	2,382	345	Decline in total lung capacity	344	7.6	yes (Day 523, inconvenience of inhaler)	
							Chest tightness	3			
							Cold	9, 24, 151, 319			
							Audible wheeze	51			
1022-1001-0005	Inh	36	M	1	4,108	71	URI	10	9.0	yes (Day 71, insuff clin response)	2 severe hypoglycemic events
							Hypoglycemia SAE	10			
							Hypoglycemia SAE	58			
1022-1008-0420	Inh	32	F	1	2,840	370	Flu	256	8.5		1st Ab >2,000 = 2,700 on inh ins day 279
1022-1010-0537	Inh	47	M	1	3,156	359	Cough	23	5.7		1 hypoglycemia SAE
							Hypoglycemia SAE	215			
1022-1015-0833	Inh	54	M	1	2,776	266	Dyspnea on exertion	184	7.7		
1022-	SQ	59	F	1	2,192	363	URI	171, 247	6.7		

Table 7.1.3.3.2.5 Summary Characteristics of Patients with Antibody (Ab) Levels >2,000 µU/mL by Esoterix® Assay

Pt ID	Tx	Age	Sex	DM Type	Pk[3] Ab in µU/mL	Day[1] of Pk Ab	AE	Study Day(s) of AE(s)	Last A1c (%)[2]	Early W/D?	Comment
1022-1248											
1022-1025-1425	Inh	54	F	1	27,286	14 (34)	URI	10	7.9	yes (Day 14, shortness of breath)	Ab Day 0 = 3,514 Ab Day 14 = 6,056 Ab Post-Tx Day 9 = 12,245 Ab Post-Tx Day 34 at left Ab Post-Tx Day 257 = 5,280
							Shortness of breath	14			
1022-1041-2369	Inh	23	F	1	2,340	352	Cold	1	9.6		1 severe hypoglycemic event
1022-5074-3082	Inh	51	F	1	2,063	51	Hypoglycemia SAE	4	9.5		29 severe hypoglycemic events (23 between 0100 and 0600)
1022-5154-3679	Inh	60	F	1	2,317	84	Cold	66	7.5	yes (Day 167, reason not specified)	1st Ab >2,000 = 2,067 on inh ins day 41
							Cough	85			
1027-1006-0251	Inh	27	F	1	2,456	28	URI	6, 22	9.6	yes (Day 52, reactive airways disease)	
							Severe reactive airways disease, bronchospasm	32			
							Decline in DLco	21			
1027-1012-0503	Inh	27	M	1	3,394	49	URI	8	7.2	yes (Day 49 of inh ins, due to cough)	
							Bronchitis	29			
							Cough	45			
1029-1016-0484	SQ	62	F	2	4,016	92	Flu	357	8.1		1st Ab >2,000 was 2,123 on tx day 46
							URI	54, 71			
1029-1043-2260	Inh	56	M	2	2,830	261			9.4		
1029-1101-4270	Inh	62	M	2	7,296	43	Wheezing	51	8.4		
							Cough	24			

1 # days of study treatment; if treatment stopped prior to peak Ab, includes # days off treatment in parentheses
2 last recorded on-treatment study HbA1c
3 Highest Ab level measured by Esoterix® assay; pts who had previous measurements by Mayo assay may have had an earlier peak by that assay, but only one measurement on residual sera by Esoterix® assay, or insufficient residual sera for Esoterix®

The majority of patients (89%) who had measured insulin antibodies >2,000 μU/mL by the Esoterix® assay were Type 1 patients (33 Type 1 vs 4 Type 2). In the overall Phase 2/3 study population, 1,209/2,787 patients (43%) had Type 1 diabetes. Pediatric patients comprised 33% (11/33) of the Type 1 patients with high antibody titres. In the overall Phase 2/3 study population, 291/1,209 (24%) of the Type 1 patients were children. Among Type 1 patients with high antibody titres, 24/33 (73%) were female. In the overall Phase 2/3 Type 1 population, 405/918 (44%) were female.

A total of 67 severe hypoglycemic events were reported in 9 patients out of the 33 Type 1 patients who had Esoterix® antibody titres >2,000 μU/mL. These 9 patients represent 27.3% of the group of Type 1 patients who had high antibody titres. In the overall controlled Type 1 Phase 2/3 patient population, 121/698 patients (17.3%) had one or more severe hypoglycemic events. Total exposure among the 33 Type 1 patients who had Exoterix® antibody titres was 618.1 months; the event rate for severe hypoglycemic events was 0.11 events per month. When excluding the 29 events that occurred in a single patient, this event rate becomes 0.06 events per month of exposure. In the overall Type 1 Phase 2/3 patient population, there were 6,138 severe hypoglycemic events over 5,626.7 patient-months, for an event rate of 1.09 events/1,000 months of exposure. When considering severe hypoglycemic events on a per patient basis, these events appear to have been more common in patients who had high insulin antibody titres than among the general study population. When considering severe hypoglycemic events on a person-time basis, these events do not appear to have occurred more commonly per unit of patient-time for patients with high insulin antibody titres than for patients in the general study population.

7.1.3.3.2.6 Was there evidence that these antibodies could neutralize the action of insulin?

The applicant reports that they made extensive attempts to develop a neutralizing antibody bioassay, but were unable to do so.

The development of neutralizing antibodies might be signaled by an increase in insulin requirement after antibodies appear. In order to look at this question with available data, Dr. Mele examined insulin antibodies and insulin doses in Study 107, the intensive control trial in Type 1 diabetics. The assumption was made that titration would be complete by month 3, with only minor increases in mean total daily insulin requirement after that. The assumption was also made that insulin antibodies would have appeared by that time, and that any effect they would have on neutralization of insulin action would be present. Antibody levels in inhaled insulin patients across the development program generally increased most rapidly during the first 6 months of treatment. Dr. Mele looked for a correlation between the change in insulin dose from Month 3 to Month 6, and insulin antibody levels. Her analysis revealed no correlation.

The applicant analyzed for associations between insulin antibody levels and overall doses of insulins (short- and long- acting), and found no association.

7.1.3.3.2.7 Was there evidence that these antibodies could have other effects on insulin pharmacodynamics or overall glycemic control?

The applicant provided scatter plots of insulin antibody levels vs indices of glycemic control. No significant association was demonstrated between insulin antibody levels and HbA1c, postprandial glucose, fasting glucose, or insulin requirement.

7.1.3.3.2.8 What happened to insulin antibody levels after discontinuation of inhaled insulin?

In Study 1027, discontinuation of inhaled insulin therapy resulted in a decrease in insulin antibody levels, although they did not return to baseline levels by 12 weeks of followup.

Table 7.1.3.3.2.8 Change from Baseline in Insulin Antibody Levels During and After Study Drug Administration in Study 1027

	Baseline and Change from Baseline Serum Antibody Level (µU/mL)* (N) [SD]			
	Mean		Median	
Time Point	INH	SC	INH	SC
Baseline values	**17.1 (97) [40.6]**	**17.4 (99) [54.4]**	**2.4**	**2.7**
Change from baseline				
Comparative phase				
Week 1	-0.5 (90) [5.8]	-0.1 (89) [8.9]	0.0	0.0
Week 2	5.3 (87) [22.7]	-1.1 (85) [6.0]	0.0	0.0
Week 4	28.7 (94) [79.6]	0.2 (89) [5.3]	5.6	0.0
Week 8	93.2 (97) [356.0]	3.2 (96) [25.3]	15.0	0.0
Week 12	112.9 (91) [218.1]	2.9 (95) [19.4]	28.0	0.0
Follow-up phase†				
Week 2	83.1 (87) [163.7]	2.3 (88) [21.1]	27.0	0.0
Week 4	61.8 (84) [122.6]	3.8 (92) [25.5]	19.5	0.0
Week 8	42.2 (85) [74.7]	4.1 (92) [25.3]	19.0	0.0
Week 12	33.3 (85) [61.7]	5.2 (93) [33.9]	13.0	0.0

*Values less than the limit of quantitation (2.1 µU/mL) were imputed as 1.05 µU/mL.
†All subjects received subcutaneous insulin as the only short-acting insulin during the follow-up phase.
N=number of subjects evaluated for antibody levels at baseline and the noted time point, SD=standard deviation, INH=inhaled insulin, and SC=subcutaneous short-acting insulin.
Source: Study 1027 Tables 12.1.1.3, 12.1.2.3, and 12.1.2.4

Source: Applicant's Table 5, Section 5.3.5.3.2

7.1.3.3.2.9 Summary of Insulin Antibody Observations

For both Type 1 and Type 2 diabetics, inhaled insulin was associated with higher end-of-study insulin antibody levels, and with greater changes from baseline in insulin antibody levels, than those seen with comparator agents. Type 1 diabetics had greater changes than Type 2 patients. Among Type 1 diabetics, pediatric patients had higher insulin antibody levels and greater change from baseline than adults. Among Type 1 patients, females had higher insulin antibody levels and greater changes from baseline than did males. Among Type 2 patients, patients who were age 65 years or older tended to have higher values in longer studies, and in studies using the

quantitative Esoterix® assay, mean antibody levels appeared to correlate with age group up to age 74 years. Seroconversion from an undetectable level of insulin antibodies at the beginning of study to detectable levels of insulin antibody at end-of-study was much more common among inhaled insulin patients (Type 1 and Type 2) than among comparator patients. Type 1 diabetics had significantly higher rates of seroconversion than Type 2 diabetics. Among Type 1 diabetics, rates of seroconversion were higher among pediatric patients than among adult patients.

Insulin antibodies appeared to be predominantly IgG, and tended to have a low affinity, high capacity binding profile.

There were no apparent associations between insulin antibody levels and occurrence of allergic events or severe hypoglycemic events. There were no apparent associations between insulin antibody levels and indices of glycemic control, such as HbA1c, postprandial glucose and fasting glucose. Evidence was not found of a neutralizing effect of these antibodies on the action of insulin; there was no association between antibody levels and requirements for either long- or short- acting insulin at last observation. In Study 107, there was no evidence of an association between insulin antibody levels and changes in insulin requirements from months 3 to 6 of study.

After discontinuation of inhaled insulin, antibody levels appeared to decline, but had not returned to baseline by 12 weeks after discontinuation.

Although inhaled insulin patients demonstrate a brisk increase in insulin antibody levels, studies to date do not demonstrate a clinical correlate of this finding.

7.1.3.3.3 Serious Herniae and Rupture Events

Because cough was a very common adverse event among inhaled insulin patients, the clinical reviewer examined events which could result from increased intrathoracic and intraabdominal pressure, such as herniae and suture rupture events. Numbers of these events are summarized in the following table:

Table 7.1.3.3.3 Incidence of Serious Herniae and Serious Rupture Events

	Inh Ins	SQ	OA
Adult Type 1 Diabetics, Controlled Ph 2/3	2 (0.2 events/100 pts)	0	n/a
Adult Type 1 Diabetics, All Ph 2/3	1 (<0.1 event/100 pt-yrs)	0	n/a
Adult Type 2 Diabetics, Controlled Ph 2/3	4 (0.3 events/100 pts)	2 (0.4 events/100 pts)	1 (0.2 events/100 pts)
Adult Type 2 Diabetics, All Ph 2/3	6 (<0.1 event/ 100 pt-yrs)	4 (<0.1 event/ 100pt-yrs)	1 (<0.1 event/ 100 pt-yrs)
Pediatric Type 1 Diabetics	0	0	n/a

Serious herniae and serious rupture events did not occur with greater frequency among patients receiving inhaled insulin than among patients receiving comparator treatments.

7.1.4 Other Search Strategies

Please see Section 7.1.2 for explorations for patterns of serious adverse event groupings for events related to severe hypoglycemia consequences, and cardiovascular adverse events.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Protocols specified that all observed or volunteered adverse events, regardless of treatment group or suspected causal relationship to study drug, were to be recorded as adverse events.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Narratives were not available for individual cases of common adverse events. When information on nonserious adverse events was included in narratives for serious adverse events, pulmonary events, or high antibody titres, event categorization appeared appropriate.

7.1.5.3 Incidence of common adverse events

In controlled Phase 2/3 studies in Type 1 diabetics, the overall incidence of adverse events was similar between inhaled insulin patients and SQ patients, with 99.4% and 98.7% of patients, respectively, experiencing some type of adverse event. In controlled Phase 2/3 studies in Type 2 patients, adverse events occurred with nearly equal frequency between inhaled insulin patients [93.7% with event(s)] and SQ patients [96.7% with event(s)]. Among Type 2 patients treated with oral agents, 81.7% experienced an adverse event. This lower rate among oral-agent treated patients is due to a lower rate of hypoglycemia among these patients than among inhaled insulin or SQ patients.

7.1.5.4 Common adverse event tables

The following tables include common adverse events; separate tables are provided for adult Type 1, adult Type 2, and pediatric Type 1 patients.

7.1.5.4.1 All-causality Common Adverse Events Occurring in ≥ 1% of Type 1 Patients, Controlled Phase 2/3 Studies, Cut-off 23 Aug 04

COSTART Body System	COSTART Event Term	Inh Ins n = 698 n (%)	SQ n = 705 n (%)
Body as a whole	**Abdominal pain**	23 (3.3)	29 (4.1)
	Abscess	4 (0.6)	10 (1.4)
	Accidental injury	77 (11.0)	80 (11.3)
	Allergic reaction	31 (4.4)	23 (3.3)
	Asthenia	81 (11.6)	85 (12.1)
	Back pain	38 (5.4)	37 (5.2)
	Chest pain	24 (3.4)	9 (1.3)

7.1.5.4.1 All-causality Common Adverse Events Occurring in ≥ 1% of Type 1 Patients, Controlled Phase 2/3 Studies, Cut-off 23 Aug 04

COSTART Body System	COSTART Event Term	Inh Ins n = 698 n (%)	SQ n = 705 n (%)
	Fever	8 (1.1)	5 (0.7)
	Flu syndrome	105 (15.0)	107 (15.2)
	Headache	105 (15.0)	110 (15.6)
	Infection	25 (3.6)	27 (3.8)
	Malaise	8 (1.1)	11 (1.6)
	Neck pain	5 (0.7)	10 (1.4)
	Pain	36 (5.2)	34 (4.8)
Cardiovascular	Hypertension	20 (2.9)	14 (2.0)
	Migraine	12 (1.7)	13 (1.8)
	Palpitation	10 (1.4)	5 (0.7)
	Syncope	3 (0.4)	7 (1.0)
	Tachycardia	14 (2.0)	12 (1.7)
	Vasodilation	10 (1.4)	9 (1.3)
Digestive	Constipation	5 (0.7)	9 (1.3)
	Diarrhea	50 (7.2)	35 (5.0)
	Dry mouth	16 (2.3)	2 (0.3)
	Dyspepsia	23 (3.3)	15 (2.1)
	Gastritis	10 (1.4)	6 (0.9)
	Gastroenteritis	34 (4.9)	36 (5.1)
	Gingivitis	3 (0.4)	9 (1.3)
	Increased appetite	27 (3.9)	41 (5.8)
	Nausea	58 (8.3)	46 (6.5)
	Tooth caries	5 (0.7)	7 (1.0)
	Tooth disorder	15 (2.1)	22 (3.1)
	Vomiting	33 (4.7)	26 (3.7)
Hemic and lymphatic	Anemia	2 (0.3)	10 (1.4)
	Bruise	6 (0.9)	11 (1.6)
Metabolic and nutritional	Hyperglycemia	13 (1.9)	3 (0.4)
	Hypoglycemia	676 (96.8)	677 (96.0)
	Peripheral edema	15 (2.1)	12 (1.7)
Musculoskeletal	Arthralgia	43 (6.2)	32 (4.5)
	Arthrosis	8 (1.1)	1 (0.1)
	Bone fracture accidental	21 (3.0)	17 (2.4)
	Bone pain	9 (1.3)	16 (2.3)
	Myalgia	9 (1.3)	16 (2.3)
	Synovitis	4 (0.6)	9 (1.3)
	Tenosynovitis	10 (1.4)	15 (2.1)
Nervous	Agitation	8 (1.1)	2 (0.3)
	Anxiety	49 (7.0)	39 (5.5)
	Carpal tunnel syndrome	7 (1.0)	9 (1.3)
	Confusion	25 (3.6)	36 (5.1)
	Depression	9 (1.3)	23 (3.3)
	Dizziness	58 (8.3)	51 (7.2)
	Hypertonia	2 (0.3)	7 (1.0)
	Hypesthesia	22 (3.2)	25 (3.5)
	Insomnia	23 (3.3)	14 (2.0)
	Nervousness	18 (2.6)	18 (2.6)
	Paresthesia	22 (3.2)	15 (2.1)
	Somnolence	11 (1.6)	10 (1.4)
	Thinking abnormal	16 (2.3)	13 (1.8)
	Tremor	122 (17.5)	127 (18.0)
Respiratory	Asthma	7 (1.0)	8 (1.1)
	Bronchitis	20 (2.9)	27 (3.8)
	Cough increased	196 (28.1)	59 (8.4)
	Dyspnea	27 (3.9)	4 (0.6)
	Epistaxis	9 (1.3)	2 (0.3)
	Laryngitis	8 (1.1)	3 (0.4)

7.1.5.4.1 All-causality Common Adverse Events Occurring in ≥ 1% of Type 1 Patients, Controlled Phase 2/3 Studies, Cut-off 23 Aug 04

COSTART Body System	COSTART Event Term	Inh Ins n = 698 n (%)	SQ n = 705 n (%)
	Pharyngitis	123 (17.6)	103 (14.6)
	Pneumonia	5 (0.7)	7 (0.1)
	Respiratory disorder	45 (6.4)	27 (3.8)
	Respiratory tract infection	290 (41.5)	279 (39.6)
	Rhinitis	96 (13.8)	67 (9.5)
	Sinusitis	64 (9.2)	48 (6.8)
	Sputum increased	27 (3.9)	8 (1.1)
Skin and appendages	Fungal dermatitis	7 (1.0)	11 (1.6)
	Herpes simplex	6 (0.9)	9 (1.3)
	Nail disorder	10 (1.4)	11 (1.6)
	Pruritis	2 (0.3)	9 (1.3)
	Rash	18 (2.6)	15 (2.1)
	Skin ulcer	1 (0.1)	7 (1.0)
	Sweating	60 (8.6)	74 (10.5)
Special senses	Abnormal vision	22 (3.2)	19 (2.7)
	Conjunctivitis	13 (1.9)	9 (1.3)
	Ear pain	8 (1.1)	11 (1.6)
	Otitis media	4 (0.6)	8 (1.1)
	Retinal disorder	6 (0.9)	11 (1.6)
Urogenital	Dysmenorrhea	6 (1.9)	7 (2.2)
	Menorrhagia	1 (0.3)	4 (1.3)
	Menstrual disorder	6 (1.9)	2 (0.6)
	Urinary tract infection	23 (3.3)	31 (4.4)
	Vaginitis	10 (3.2)	16 (5.0)

Source: Applicant's Table 4.1.2.1.1, ISS

Hypoglycemia was the most common adverse event among Type 1 patients, and occurred with equal frequency in inhaled insulin and SQ group patients. Cough was a common adverse event, and occurred with significantly greater frequency among inhaled insulin patients (196/698, 28.1%) than among SQ patients (59/705, 8.4%). Other respiratory adverse events (dyspnea, respiratory disorder) also occurred with greater frequency among inhaled insulin patients. Nasopharyngeal adverse events (epistaxis, pharyngitis, rhinitis, sinusitis) occurred at a higher frequency in inhaled insulin groups (310/698, 44.4%) than in SQ groups (220/705, 31.2%). Adverse event terms related to accidents occurred with equal frequency between groups. The event term "allergic reaction" occurred with slightly greater numeric frequency in inhaled insulin patients (31/698, 4.4%) than among SQ patients (23/705, 3.3%).

The following table lists adverse events occurring with a frequency at least 2% greater in inhaled insulin patients compared to SQ patients.

Table 7.1.5.4.2 Adverse Events Occurring with a Frequency at least 2% Greater in Inhaled Insulin Patients Compared to SQ Patients, Type 1 Patients, Controlled Phase 2 and Phase 3 Trials, Cut-off 23 Aug 03

COSTART Body System	COSTART Event Term	Inh Ins n = 698 n (%)	SQ n = 705 n (%)
Body as a whole	Chest pain	24 (3.4)	9 (1.3)
Digestive	Diarrhea	50 (7.2)	35 (5.0)
	Dry mouth	16 (2.3)	2 (0.3)

Table 7.1.5.4.2 Adverse Events Occurring with a Frequency at least 2% Greater in Inhaled Insulin Patients Compared to SQ Patients, Type 1 Patients, Controlled Phase 2 and Phase 3 Trials, Cut-off 23 Aug 03

COSTART Body System	COSTART Event Term	Inh Ins n = 698 n (%)	SQ n = 705 n (%)
Respiratory	Cough increased	196 (28.1)	59 (8.4)
	Dyspnea	27 (3.9)	4 (0.6)
	Pharyngitis	123 (17.6)	103 (14.6)
	Respiratory disorder	45 (6.4)	27 (3.8)
	Rhinitis	96 (13.8)	67 (9.5)
	Sinusitis	64 (9.2)	48 (6.8)
	Sputum increased	27 (3.9)	8 (1.1)

Source: Applicant's Table 4.1.2.1.1, ISS

The following table lists common adverse events occurring in Type 2 patients in controlled Phase 2/3 trials.

7.1.5.4.3 All-causality Common Adverse Events Occurring in ≥ 1% of Type 2 Patients, Controlled Phase 2/3 Studies, Cut-off 23 Aug 04

COSTART Body System	COSTART Event Term	Inh Ins n = 1277 SME = 12186 n (%)	SQ n = 488 SME = 4868 n (%)	OA n = 644 SME = 6452 n (%)
Body as a whole	**Abdominal pain**	49 (3.8)	16 (3.3)	40 (6.2)
	Abscess	13 (1.0)	8 (1.6)	5 (0.8)
	Accidental injury	98 (7.7)	55 (11.3)	41 (6.4)
	Allergic reaction	30 (2.3)	12 (2.5)	12 (1.9)
	Asthenia	155 (12.1)	65 (13.3)	59 (9.2)
	Back pain	97 (7.6)	53 (10.9)	40 (6.2)
	Cellulitis	16 (1.3)	6 (1.2)	5 (0.8)
	Chest pain	56 (4.4)	15 (3.1)	21 (3.3)
	Fever	17 (1.3)	4 (0.8)	10 (1.6)
	Flu syndrome	165 (12.9)	62 (12.7)	59 (9.2)
	Headache	164 (12.8)	33 (6.8)	67 (10.4)
	Infection	24 (1.9)	15 (3.1)	19 (3.0)
	Malaise	25 (2.0)	3 (0.6)	20 (3.1)
	Neck pain	13 (1.0)	7 (1.4)	4 (0.6)
	Neoplasm	11 (0.9)	6 (1.2)	2 (0.3)
	Pain	89 (7.0)	40 (8.2)	35 (5.4)
Cardiovascular	**Angina pectoris**	12 (0.9)	2 (0.4)	16 (2.5)
	Atrial fibrillation	3 (0.2)	5 (1.0)	1 (0.2)
	Hypertension	106 (8.3)	39 (8.0)	49 (7.6)
	Palpitation	16 (1.3)	9 (1.8)	10 (1.6)
	Tachycardia	21 (1.6)	9 (1.8)	5 (0.8)
	Vasodilation	10 (0.8)	7 (1.4)	3 (0.5)
Digestive	**Constipation**	22 (1.7)	4 (0.8)	16 (2.5)
	Diarrhea	88 (6.9)	28 (5.7)	68 (10.6)
	Dry mouth	32 (2.5)	2 (0.4)	9 (1.4)
	Dyspepsia	61 (4.8)	27 (5.5)	31 (4.8)
	Flatulence	12 (0.9)	3 (0.6)	13 (2.0)
	Gastritis	16 (1.3)	6 (1.2)	12 (1.9)
	Gastroenteritis	33 (2.6)	16 (3.3)	13 (2.0)
	Gingivitis	15 (1.2)	6 (1.2)	6 (0.9)
	Increased appetite	54 (4.2)	22 (4.5)	20 (3.1)
	Nausea	79 (6.2)	25 (5.1)	33 (5.1)
	Tooth disorder	24 (1.9)	10 (2.0)	16 (2.5)
	Vomiting	32 (2.5)	15 (3.1)	23 (3.6)
Endocrine	**Goiter**	2 (0.2)	7 (1.4)	3 (0.5)

7.1.5.4.3 All-causality Common Adverse Events Occurring in ≥ 1% of Type 2 Patients, Controlled Phase 2/3 Studies, Cut-off 23 Aug 04

COSTART Body System	COSTART Event Term	Inh Ins n = 1277 SME = 12186 n (%)	SQ n = 488 SME = 4868 n (%)	OA n = 644 SME = 6452 n (%)
Hemic and lymphatic	Anemia	12 (0.9)	3 (0.6)	9 (1.4)
Metabolic and nutritional	Hypercholesterolemia	11 (0.9)	5 (1.0)	7 (1.1)
	Hyperlipemia	24 (1.9)	8 (1.6)	22 (3.4)
	Hypoglycemia	794 (62.2)	360 (73.8)	185 (28.7)
	Peripheral edema	71 (5.6)	28 (5.7)	27 (4.2)
	Weight gain	23 (1.8)	5 (1.0)	7 (1.1)
Musculoskeletal	Arthralgia	84 (6.6)	41 (8.4)	39 (6.1)
	Arthritis	24 (1.9)	21 (4.3)	13 (2.0)
	Arthrosis	17 (1.3)	5 (1.0)	9 (1.4)
	Bone fracture accidental	26 (2.0)	11 (2.3)	10 (1.6)
	Leg cramps	9 (0.7)	10 (2.0)	12 (1.9)
	Myalgia	27 (2.1)	16 (3.3)	17 (2.6)
	Tenosynovitis	20 (1.6)	4 (0.8)	8 (1.2)
Nervous	Agitation	7 (0.5)	8 (1.6)	2 (0.3)
	Anxiety	53 (4.2)	33 (6.8)	15 (2.3)
	Carpal tunnel syndrome	10 (0.8)	6 (1.2)	6 (0.9)
	Confusion	17 (1.3)	18 (3.7)	2 (0.3)
	Depression	36 (2.8)	22 (4.5)	23 (3.6)
	Dizziness	140 (11.0)	63 (12.9)	38 (5.9)
	Hypesthesia	24 (1.9)	23 (4.7)	10 (1.6)
	Insomnia	29 (2.3)	14 (2.9)	12 (1.9)
	Muscular hypertonia	8 (0.6)	5 (1.0)	1 (0.2)
	Nervousness	33 (2.6)	16 (3.3)	4 (0.6)
	Neuropathy	24 (1.9)	11 (2.3)	16 (2.5)
	Paresthesia	55 (4.3)	8 (1.6)	19 (3.0)
	Somnolence	25 (2.0)	7 (1.4)	10 (1.6)
	Tremor	212 (16.6)	93 (19.1)	58 (9.0)
	Vertigo	23 (1.8)	1 (0.2)	5 (0.8)
Respiratory	Asthma	25 (2.0)	8 (1.6)	3 (0.5)
	Bronchitis	61 (4.8)	17 (3.5)	26 (4.0)
	Cough increased	268 (21.0)	36 (7.4)	24 (3.7)
	Dyspnea	42 (3.3)	9 (1.8)	9 (1.4)
	Epistaxis	15 (1.2)	2 (0.4)	5 (0.8)
	Pharyngitis	119 (9.3)	43 (8.8)	38 (5.9)
	Pneumonia	11 (0.9)	6 (1.2)	4 (0.6)
	Respiratory disorder	65 (5.1)	41 (8.4)	11 (1.7)
	Respiratory tract infection	357 (28.0)	166 (34.0)	127 (19.7)
	Rhinitis	103 (8.1)	46 (9.4)	19 (3.0)
	Sinusitis	65 (5.1)	41 (8.4)	15 (2.3)
Skin and appendages	Dermatitis	2 (0.2)	5 (1.0)	1 (0.2)
	Fungal dermatitis	18 (1.4)	3 (0.6)	1 (0.2)
	Herpes zoster	14 (1.1)	2 (0.4)	1 (0.2)
	Nail disorder	16 (1.3)	18 (3.7)	4 (0.6)
	Pruritus	24 (1.9)	3 (0.6)	12 (1.9)
	Rash	51 (4.0)	21 (4.3)	13 (2.0)
	Skin disorder	11 (0.9)	8 (1.6)	3 (0.5)
	Skin ulcer	14 (1.1)	9 (1.8)	5 (0.8)
	Sweating	146 (11.4)	60 (12.3)	42 (6.5)
Special senses	Abnormal vision	52 (4.1)	20 (4.1)	18 (2.8)
	Cataract	20 (1.6)	2 (0.4)	7 (1.1)
	Conjunctivitis	16 (1.3)	8 (1.6)	8 (1.2)
	Ear disorder	9 (0.7)	6 (1.2)	2 (0.3)
	Ear pain	12 (0.9)	7 (1.4)	3 (0.5)
	Otitis media	8 (0.6)	9 (1.8)	2 (0.3)
	Retinal disorder	48 (3.8)	7 (1.4)	34 (5.3)

7.1.5.4.3 All-causality Common Adverse Events Occurring in ≥ 1% of Type 2 Patients, Controlled Phase 2/3 Studies, Cut-off 23 Aug 04

COSTART Body System	COSTART Event Term	Inh Ins n = 1277 SME = 12186 n (%)	SQ n = 488 SME = 4868 n (%)	OA n = 644 SME = 6452 n (%)
Urogenital	Cystitis	6 (0.5)	6 (1.2)	6 (0.9)
	Impotence	15 (1.9)	2 (0.7)	11 (3.0)
	Menstrual disorder	1 (0.2)	1 (0.6)	3 (1.1)
	Metrorrhagia	0	0	4 (1.4)
	Prostatic disorder	8 (1.0)	0	3 (0.8)
	Urinary tract infection	50 (3.9)	25 (5.1)	24 (3.7)
	Vaginitis	13 (2.7)	1 (0.6)	9 (3.2)

Source: Applicant's Table 4.1.2.1.2, Section 2.7.4

Hypoglycemia was the most common adverse event term, and occurred most commonly in SQ patients (360/488, 73.8%). Inhaled insulin patients had a lower rate of hypoglycemic events than SQ patients, but had a higher rate than OA patients [inh ins = 794/1277 (62.2%), OA = 185/644 (28.7%)]. Cough was also very common, and occurred with significantly higher frequency among inhaled insulin patients than among comparator patients (inh ins 21.0%, SQ 7.4%, OA 3.7%). Accident and injury terms occurred numerically more frequently among SQ patients than among other groups. Several respiratory events (e.g. asthma, bronchitis, dyspnea) had a somewhat higher frequency among inhaled insulin patients than among comparator patients; please see Dr. Seymour's pulmonary review for discussion. Headache and paresthesia occurred at a slightly higher numeric rate in inhaled insulin groups than in comparator groups.

The following table includes those events which occurred in Type 2 inhaled insulin patients at a frequency >2% higher than the frequency seen in a comparator group.

Table 7.1.5.4.4 All-causality Adverse Events Occurring in Inhaled Insulin Patients at a Frequency >2% Higher than the Frequency Seen in a Comparator Group, Type 2 Controlled Phase 2/3 Trials, Cut-off 23 Aug 04

COSTART Body System	COSTART Event Term	Inh Ins n = 1277 n (%)	SQ n = 488 n (%)	OA n = 644 n (%)
Body as a whole	Asthenia	155 (12.1)	65 (13.3)	59 (9.2)
	Flu syndrome	165 (12.9)	62 (12.7)	59 (9.2)
	Headache	164 (12.8)	33 (6.8)	67 (10.4)
Digestive	Dry mouth	32 (2.5)	2 (0.4)	9 (1.4)
Metabolic and nutritional	Hypoglycemia	794 (62.2)	360 (73.8)	185 (28.7)
Nervous	Dizziness	140 (11.0)	63 (12.9)	38 (5.9)
	Nervousness	33 (2.6)	16 (3.3)	4 (0.6)
	Paresthesia	55 (4.3)	8 (1.6)	19 (3.0)
	Tremor	212 (16.6)	93 (19.1)	58 (9.0)
Respiratory	Cough increased	268 (21.0)	36 (7.4)	24 (3.7)
	Pharyngitis	119 (9.3)	43 (8.8)	38 (5.9)
	Respiratory disorder	65 (5.1)	41 (8.4)	11 (1.7)
	Respiratory tract infection	357 (28.0)	166 (34.0)	127 (19.7)
	Rhinitis	103 (8.1)	46 (9.4)	19 (3.0)
	Sinusitis	65 (5.1)	41 (8.4)	15 (2.3)
Skin and appendages	Rash	51 (4.0)	21 (4.3)	13 (2.0)
	Sweating	146 (11.4)	60 (12.3)	42 (6.5)
	Retinal disorder	48 (3.8)	7 (1.4)	34 (5.3)

Table 7.1.5.4.4 All-causality Adverse Events Occurring in Inhaled Insulin Patients at a Frequency >2% Higher than the Frequency Seen in a Comparator Group, Type 2 Controlled Phase 2/3 Trials, Cut-off 23 Aug 04

COSTART Body System	COSTART Event Term	Inh Ins n = 1277 n (%)	SQ n = 488 n (%)	OA n = 644 n (%)
	Vaginitis	13 (2.7)	1 (0.6)	9 (3.2)

Source: Applicant's Table 4.1.2.1.2, Section 2.7.4

The following table lists common adverse events occurring in pediatric patients.

Table 7.1.5.4.5 All-causality Common Adverse Events Occurring in ≥ 1% of Pediatric Patients, Controlled Phase 2/3 Studies, Cut-off 1 Aug 03

COSTART Body System	COSTART Event Term	Inh Ins n = 153 n (%)	SQ n = 148 n (%)
Body as a whole	Abdominal pain	17 (11.1)	11 (7.4)
	Accidental injury	23 (15.0)	27 (18.2)
	Allergic reaction	6 (3.9)	3 (2.0)
	Appl/inj/incis/insertion site pain	6 (3.9)	3 (2.0)
	Asthenia	35 (22.9)	33 (22.3)
	Back pain	7 (4.6)	5 (3.4)
	Chest pain	5 (3.3)	0
	Face edema	1 (0.7)	5 (3.4)
	Fever	2 (1.3)	3 (2.0)
	Flu syndrome	19 (12.4)	18 (12.2)
	Headache	45 (29.4)	35 (23.6)
	Infection	9 (5.9)	14 (9.5)
	Infection fungal	2 (1.3)	1 (0.7)
	Pain	6 (3.9)	5 (3.4)
Cardiovascular	Migraine	1 (0.7)	2 (1.4)
	Pallor	1 (0.7)	3 (2.0)
	Vasodilation	2 (1.3)	2 (1.4)
Digestive	Anorexia	2 (1.3)	1 (0.7)
	Diarrhea	1 (0.7)	4 (2.7)
	Dry mouth	3 (2.0)	0
	Dyspepsia	2 (1.3)	4 (2.7)
	Flatulence	0	2 (1.4)
	Gastritis	4 (2.6)	2 (1.4)
	Gastroenteritis	3 (2.0)	6 (4.1)
	Gastrointestinal disorder	3 (2.0)	2 (1.4)
	Increased appetite	12 (7.8)	11 (7.4)
	Nausea	14 (9.2)	5 (3.4)
	Tooth disorder	1 (0.7)	2 (1.4)
	Vomiting	17 (11.1)	13 (8.8)
Hemic and lymphatic	Bruise	7 (4.6)	5 (3.4)
	Lymphadenopathy	4 (2.6)	3 (2.0)
Metabolic and nutritional	Albuminuria	2 (1.3)	0
	Hyperglycemia	2 (1.3)	1 (0.7)
	Hyperlipemia	0	2 (1.4)
	Hypoglycemia	152 (99.3)	146 (98.6)
	Ketosis	7 (4.6)	6 (4.1)
	Lipodystrophy	2 (1.3)	4 (2.7)
Musculoskeletal	Arthralgia	8 (5.2)	4 (2.7)
	Bone fracture accidental	9 (5.9)	2 (1.4)
	Myalgia	2 (1.3)	1 (0.7)
	Myasthenia	2 (1.3)	0
Nervous	Anxiety	2 (1.3)	1 (0.7)

Table 7.1.5.4.5 All-causality Common Adverse Events Occurring in ≥ 1% of Pediatric Patients, Controlled Phase 2/3 Studies, Cut-off 1 Aug 03

COSTART Body System	COSTART Event Term	Inh Ins n = 153 n (%)	SQ n = 148 n (%)
	Confusion	8 (5.2)	2 (1.4)
	Convulsion	0	2 (1.4)
	Depression	1 (0.7)	2 (1.4)
	Dizziness	22 (14.4)	14 (9.5)
	Hypertonia	1 (0.7)	2 (1.4)
	Hypesthesia	4 (2.6)	0
	Nervousness	2 (1.3)	2 (1.4)
	Paresthesia	3 (2.0)	1 (0.7)
	Somnolence	2 (1.3)	6 (4.1)
	Thinking abnormal	0	2 (1.4)
	Tremor	51 (33.3)	49 (33.1)
Respiratory	Asthma	3 (2.0)	5 (3.4)
	Cough increased	48 (31.4)	14 (9.5)
	Dyspnea	5 (3.3)	0
	Epistaxis	3 (2.0)	3 (2.0)
	Laryngitis	0	2 (1.4)
	Pharyngitis	34 (22.2)	31 (20.9)
	Pneumonia	0	2 (1.4)
	Respiratory disorder	12 (7.8)	10 (6.8)
	Respiratory tract infection	59 (38.6)	57 (38.5)
	Rhinitis	24 (15.7)	31 (20.9)
	Sinusitis	5 (3.3)	11 (7.4)
	Sputum increased	2 (1.3)	2 (1.4)
Skin and appendages	Acne	3 (2.0)	2 (1.4)
	Fungal dermatitis	1 (0.7)	2 (1.4)
	Herpes simplex	1 (0.7)	2 (1.4)
	Maculopapular rash	2 (1.3)	1 (0.7)
	Nail disorder	2 (1.3)	1 (0.7)
	Pruritus	2 (1.3)	1 (0.7)
	Rash	7 (4.6)	6 (4.1)
	Skin benign neoplasm	3 (2.0)	4 (2.7)
	Skin disorder	1 (0.7)	3 (2.0)
	Skin hypertrophy	1 (0.7)	5 (3.4)
	Sweating	14 (9.2)	5 (3.4)
Special senses	Abnormal vision	5 (3.3)	2 (1.4)
	Blepharitis	0	2 (1.4)
	Conjunctivitis	4 (2.6)	6 (4.1)
	Ear disorder	2 (1.3)	0
	Ear pain	6 (3.9)	2 (1.4)
	Otitis media	10 (6.5)	5 (3.4)
Urogenital	Dysmenorrhea	3 (3.9% of ♀)	2 (2.9% of ♀)
	Penis disorder	1 (1.3% of ♂)	1 (1.3% of ♂)
	Urinary tract infection	3 (2.0)	0
	Vaginitis	1 (1.3% of ♀)	1 (1.4% of ♀)

Source: Applicant's Table 4.1.1.1.1.1.2, Section 2.7.4, ISS

The following adverse event terms occurred at a frequency at least 2% higher among pediatric inhaled insulin patients than among SQ patients.

Table 7.1.5.4.6 Adverse Events Occurring at a Frequency at Least 2% Greater in Inhaled Insulin Patients than in SQ Patients, Type 1 DM, <18 Years of Age

COSTART Body System	COSTART Event Term	Inh Ins n = 153 n (%)	SQ n = 148 n (%)
Body as a whole	Abdominal pain	17 (11.1)	11 (7.4)
	Headache	45 (29.4)	35 (23.6)
Digestive	Dry mouth	3 (2.0)	0
	Nausea	14 (9.2)	5 (3.4)
	Vomiting	17 (11.1)	13 (8.8)
Musculoskeletal	Arthralgia	8 (5.2)	4 (2.7)
	Bone fracture accidental	9 (5.9)	2 (1.4)
Nervous	Confusion	8 (5.2)	2 (1.4)
	Dizziness	22 (14.4)	14 (9.5)
	Hypesthesia	4 (2.6)	0
Respiratory	Cough increased	48 (31.4)	14 (9.5)
Skin and appendages	Sweating	5 (3.3)	2 (1.4)
Special senses	Ear pain	6 (3.9)	2 (1.4)
	Otitis media	10 (6.5)	5 (3.4)

Source: Applicant's Table 4.1.1.1.1.1.2, ISS

Overall hypoglycemic event rates (for serious and nonserious events) did not differ between pediatric inhaled insulin and SQ patients. The adverse event term seen with the greatest excess frequency for inhaled over SQ was cough. Nausea, headache and dizziness also occurred numerically more frequently in inhaled insulin patients than in SQ patients.

When combining ear terms, adverse events related to the ear occurred more frequently in children in inhaled insulin groups than in SQ groups. The terms ear pain, ear disorder and otitis media had a combined event rate of 18/153 (11.8%) in the inhaled insulin patients vs 7/148 (4.7%) in SQ patients. This difference could be due to chance; however, the Eustachian tube in children provides an anatomically more direct route to the middle ear than does the Eustachian tube of the adult, and the possibility of entry of inhalation powder into the Eustachian tube of children is a consideration.

7.1.5.5 Identifying common and drug-related adverse events

Common adverse events which seem likely to be related to inhaled insulin use include cough; nasopharyngeal adverse events such as pharyngitis, rhinitis and sinusitis; and certain respiratory adverse events such as dyspnea. Adverse events related to the ear seem to be related to inhaled insulin in children.

7.1.5.6 Additional analyses and explorations

Dr. Seymour's pulmonary review discusses respiratory adverse events. Additional analyses for rhinitis and sinusitis follow, as these events appear related to inhaled insulin use.

The following table examines the incidence of rhinitis and sinusitis by age.

Table 7.1.5.6 Incidence of Rhinitis and Sinusitis by Age, Controlled Phase 2/3 Studies

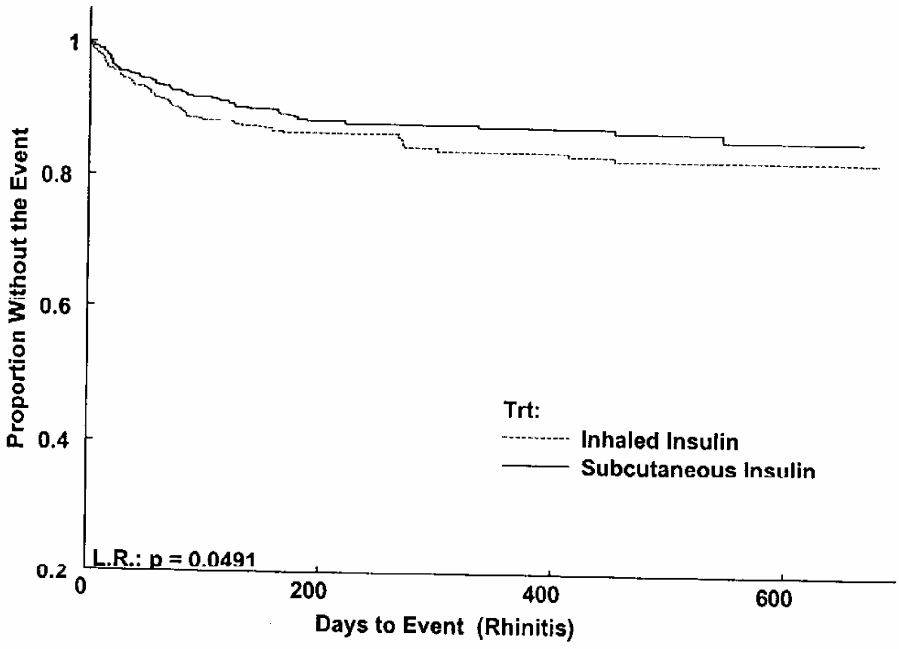
Age Group	Adverse Event	Inh Ins Grp # events (# events per 100 patients in tx grp in this age range)	SQ Grp # events (# events per 100 patients in tx grp in this age range)	OA Grp # events (# events per 100 patients in tx grp in this age range)
<18 years (Type 1)	Rhinitis	24 (20.9)	31 (20.9)	N/A
	Sinusitis	5 (3.3)	11 (7.4)	N/A
18-44 years (Type 1)	Rhinitis	72 (14.2)	52 (10.2)	N/A
	Sinusitis	44 (8.7)	37 (7.3)	N/A
18-44 years (Type 2)	Rhinitis	14 (10.9)	14 (18.7)	2 (2.8)
	Sinusitis	10 (7.7)	12 (16.0)	5 (6.9)
45-64 years (Type 1)	Rhinitis	24 (12.6)	15 (7.7)	N/A
	Sinusitis	20 (10.5)	11 (5.6)	N/A
45-64 years (Type 2)	Rhinitis	73 (8.6)	25 (8.3)	14 (3.3)
	Sinusitis	43 (5.0)	24 (7.9)	9 (2.1)
65-74 years (Type 1)	Rhinitis	0	0	N/A
	Sinusitis	0	0	N/A
65-74 years (Type 2)	Rhinitis	14 (5.3)	7 (6.9)	3 (2.5)
	Sinusitis	12 (4.5)	5 (4.9)	1 (0.8)
≥75 years (Type 2)	Rhinitis	2 (6.7)	0	0
	Sinusitis	0	0	0

Source: Applicant's Table 4.1.3.1.2, ISS; applicant's Table 4.1.1.1.1.1.2, Section 2.7.4, ISS

There is no clear relationship between age and incidence of rhinitis or sinusitis in patients exposed to inhaled insulin. For Type 1 diabetics, the highest incidence of rhinitis occurred in pediatric patients, but the incidence was equal between inhaled insulin and SQ patients. In Type 1 diabetics aged 45-64 years, rhinitis occurred more commonly among inhaled insulin patients (12.6%) than among SQ patients (7.7%). Among Type 1 diabetics treated with inhaled insulin, the highest incidence of sinusitis occurred in the age 45-64 years category, and sinusitis occurred more frequently among inhaled insulin patients in this age group than among SQ patients in this age group. Among Type 2 patients, the age category with the highest incidence of rhinitis among inhaled insulin patients was 18-44 years, but rhinitis occurred at a higher rate among SQ patients in this age group. In the age 45-64 years group of Type 2 diabetics, rhinitis occurred at a slightly higher rate among inhaled insulin patients than patients in other treatment groups. In Type 2 diabetics, the highest incidence of sinusitis among inhaled insulin patients occurred in the age 18-44 years group. There was no age group of Type 2 diabetics where the incidence of sinusitis in the inhaled insulin group exceeded the incidence of sinusitis in both other treatment groups.

Dose dependency was not demonstrated for either rhinitis or sinusitis. Time to event did not differ between inhaled insulin and comparator patients for sinusitis. However, inhaled insulin patients who developed rhinitis did so sooner than SQ patients who developed rhinitis. This is illustrated in the following Kaplan-Meier plot by Dr. Mele of Biostatistics.

Figure 7.1.5.6 Kaplan-Meier Plot for Time to Event for Rhinitis



Log-Rank chi Square = 3.871, p = 0.0491

7.1.6 Less Common Adverse Events

The clinical reviewer examined all adverse event terms in the Phase 2/3 databases (crt/datasets/ALLPH23/ae1.xpt through crt/datasets/ALLPH23/ae14.xpt) to identify relatively rare events that could be of significant concern. The following table lists events of note, and compares the incidence of these events on a person-time basis between inhaled insulin groups (all Phase 2/3) and comparator groups (controlled Phase 2/3). Comparison between the full Phase 2/3 population for inhaled insulin and the controlled Phase 2/3 population for comparator groups has limitations, and cannot be used to firmly establish a higher incidence of any of these events among inhaled insulin patients. Because many inhaled insulin patients had a much longer duration of exposure than any comparator patient, inhaled insulin group patients may have been more likely to develop events that increase in incidence with aging.

Table 7.1.6.1 Selected Uncommon Adverse Events, All Phase 2/3 Trials of Inhaled Insulin, with Comparator Rates from Controlled Phase 2/3 Trials

Body System	Applicant's Text Term for Event (PREFTEXT Column in Databases)	Inh Ins Total exposure = 47,259 months # events (# events per 1,000 months of patient exposure)	Comparator Total exposure = 17,373 months # events (# events per 1,000 months of patient exposure)
Eye	Blindness	2 (0.04)	0
	Eye hemorrhage	50 (1.06)	16 (0.92)
	Retinal detachment	4 (0.08)	1 (0.06)
	Retinal disorder	282 (5.97)	98 (5.64)
	Retinal hemorrhage	26 (0.55)	5 (0.29)
Hematologic	Leukopenia	21 (0.44)	0
Immune	Allergic reaction	284 (6.01)	83 (4.78)
Neoplasia	Bladder carcinoma	1 (0.02)	0
	Bladder neoplasm	1 (0.02)	0
	Breast carcinoma	9 (0.19)	6 (0.35)
	Breast neoplasm	14 (0.30)	7 (0.40)
	Carcinoma	2 (0.04)	7 (0.40)
	Carcinoma of lung	5 (0.11)	3 (0.17)
	Chronic myelocytic leukemia	3 (0.06)	0
	Esophageal carcinoma	1 (0.02)	0
	Gastrointestinal carcinoma	7 (0.15)	14 (0.81)
	Hepatoma	1 (0.02)	0
	Melanoma	2 (0.04)	0
	Neoplasm	40 (0.85)	27 (1.55)
	Prostate carcinoma	6 (0.13)	5 (0.29)
	Renal carcinoma	1 (0.02)	0
	Skin carcinoma	22 (0.47)	5 (0.29)
	Thyroid carcinoma	2 (0.04)	0
	Total malignant neoplastic events	58 (1.23)	40 (2.30)
	Total malignant neoplastic events excluding nonmelanoma skin carcinoma	36 (0.76)	35 (2.01)
Vascular	Arterial thrombosis	7 (0.15)	0

Source: Applicant's Databases crt/datasets/ALLPH23/ae1.xpt through crt/datasets/ALLPH23/ae14.xpt and crt/datasets/CNTPH23/ae1.xpt through crt/datasets/CNTPH23/ae9.xpt

The events "eye hemorrhage" and "retinal hemorrhage" occurred more frequently per unit of patient-time over all Phase 2/3 trials than these events occurred per unit of patient time in comparator groups in the controlled Phase 2/3 trials.

Events termed "allergic reaction" occurred at a somewhat higher frequency per unit of patient-time among inhaled insulin patients in the population of all Phase 2/3 trials than among comparator patients in the controlled Phase 2/3 trials. Concern exists for the development of undesirable immune responses to inhaled insulin.

Some events in the above table were reported more than once for a given patient. For eye hemorrhage, the clinical reviewer considered each eye hemorrhage event to possibly represent the occurrence of new pathology, and thus compared rates by numbers of events. However, for certain other events, such as malignant neoplasms, repeated events in a given patient did not likely represent the appearance of new pathology, such as a second primary malignancy of the same type. Therefore, the clinical reviewer identified the number of patients with each event, and these are listed in the following table.

Table 7.1.6.2 Numbers of Patients with Significant Adverse Events, All Phase 2/3 Trials of Inhaled Insulin, with Comparator Rates from Controlled Phase 2/3 Trials

Body System	Applicant's Text Term for Event (PREFTEXT Column in Databases)	Inh Ins Total exposure = 47,259 months # patients (# patients with event per 1,000 months of patient exposure)	Comparator Total exposure = 17,373 months # patients (# patients with event per 1,000 months of patient exposure)
Hematologic	Leukopenia (in patients not reported to have malignancy)	8 (0.17)	0
Neoplasia	Bladder carcinoma	1 (0.02)	0
	Breast carcinoma	4 (0.08)	3 (0.17)
	Carcinoma (in patients not reported to have a specific malignancy)	2 (0.04)	4 (0.23)
	Carcinoma of lung	3 (0.06)	2 (0.12)
	Chronic myelocytic leukemia	1 (0.02)	0
	Esophageal carcinoma	1 (0.02)	0
	Gastrointestinal carcinoma	5 (0.11)	7 (0.40)
	Melanoma	2 (0.04)	0
	Prostate carcinoma	6 (0.13)	3 (0.17)
	Renal carcinoma	1 (0.02)	0
	Thyroid carcinoma	1 (0.02)	0
	Total patients with malignant neoplastic events excluding nonmelanoma skin carcinoma	27 (0.57)	19 (1.09)
Vascular	Arterial thrombosis	3 (0.06)	0

Source: Applicant's Databases crt/datasets/ALLPH23/ae1.xpt through crt/datasets/ALLPH23/ae14.xpt and crt/datasets/CNTPH23/ae1.xpt through crt/datasets/CNTPH23/ae9.xpt

Malignant neoplasms did not occur with a greater frequency in inhaled insulin patients per unit of patient-time than in comparator patients.

The clinical reviewer attempted to examine cases of leukopenia and arterial thrombosis among inhaled insulin patients. The applicant had not provided narratives for any of these cases, and none of the study reports discussed events of leukopenia or arterial thrombosis. On 9 Jun 05, the clinical reviewer requested narratives or case report forms for cases of arterial thrombosis. On 14 Jul 05, Mr. Brian Green sent an email with narratives for these patients. Two of these patients (patient IDs 1001-0056-0122 and 1002-0143-8030) had worsening of underlying lower extremity peripheral vascular disease. The third patient (ID 108-5005-8067) experienced an event of "moderate occlusion bilateral distal superficial femoral arteries" and was referred to a vascular surgeon. This event continued for over a year, until the patient discontinued study due to bronchitis. Inhaled insulin does not appear to be associated with an increased risk for arterial thrombosis.

The following database information was available for inhaled insulin group patients with reported events of leukopenia:

7.1.6.3 Characteristics of Inhaled Insulin Patients with Reported Events of Leukopenia

Patient ID	Baseline WBC	First WBC < 4.1 x 10^3 cells/ mm^3	Study Day of First WBC < 4.1	Lowest WBC	Study Day of Lowest WBC	Last WBC	Study Day of Last WBC	Age at Study Entry (yrs)	Gender
102-5008-0060	3.0	3.0	BL	2.6	1462	3.6	2596	26	M
106-5030-6885	3.0	3.0	BL	2.5	521	3.6	988	42	M
106-5030-6886	3.6	3.6	BL	2.3	974	2.9	1153	28	M
107-5093-7392	7.1	3.0	877	3.0	877	4.0	996	15	F
107-5033-7829	3.6	3.6	BL	3.0	596	4.2	1038	49	M
109-5071-0073	5.1	No values <4.1	N/A	4.7	804	5.8	1079	67	F
1009-5093-3366	5.7	2.9	477	2.9	477	6.2	694	9	F
1009-5093-3359	3.4	3.4	BL	2.5	676	2.5	676	8	M

Source: Datasets ALLPH23/lab11- ALLPH23/lab19, ALLPH23/lab21- ALLPH23/lab26, ALLPH23/lab110- ALLPH23/lab 123,

Most of these patients had mild baseline leukopenia, and little change from their baseline. None of these patients became absolutely neutropenic. One of the two patients who had a normal WBC at baseline and became neutropenic recovered to a normal WBC. The other of these two patients, a 15 year old female, had recovered to just below the lower limit of normal at her last recorded WBC value. These data do not suggest an association between inhaled insulin and risk for new development of leukopenia.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

The applicant provided laboratory data for 51 Phase 2 and Phase 3 studies (31 clinical pharmacology and 20 clinical). Routine chemistry, hematology and urinalyses were collected for all patients. Databases provided did not always include laboratory collected outside routine clinical visits, e.g. laboratory collected at the time of an adverse event was not always included in databases.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Controlled Phase 2 and Phase 3 studies were used for comparisons of laboratory change and abnormalities between inhaled insulin and comparator(s).

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

The following tables list median changes from baseline in safety laboratory data.

Table 7.1.7.3.1.1 Median Change from Baseline to Last Observation, Safety Laboratory, Adult Type 1 Patients, Phase 2/3 Controlled Trials

			Inh Ins			SQ		
Lab Category	**Lab Test**	**Units**	**N**	**Baseline Median**	**Median Change from Baseline**	**N**	**Baseline Median**	**Median Change from Baseline**
Hematology	**Hemoglobin (Hb)**	**G/dL**	651	15.2	0	645	15.2	0
	Hematocrit (Hct)	**%**	600	45	0	592	45	0
	Red blood cell count (RBC)	**# cells x 10^6/mm^3**	271	4.8	-0.1	266	4.8	-0.1
	Platelets (PLT)	**# cells x 10^3/mm^3**	602	233	2	606	239	-3
	White blood cell count (WBC)	**# cells x 10^3/mm^3**	613	507	0	608	5.8	0
	Neutrophils	**%**	34	59.2	-2.9	35	60.5	-0.8
	Eosinophils	**%**	246	2.8	0.6	243	2.6	0.2
	Basophils	**%**	246	0.4	0	243	0.4	0
	Lymphocytes	**%**	34	29.7	2.55	35	26	0.8
	Monocytes	**%**	34	7.55	-0.1	35	7.3	0.3
	MCV	**10^{-15} L**	33	90	0	34	90	1
	MCH	**pG/cell**	33	31	-1	34	31	0
	MCHC	**G/dL**	33	34	0	34	34	-1
	Bands	**%**	1	11	-4	1	6	0
Liver Function	**Total bilirubin (Bili)**	**mg/dL**	608	0.5	0	610	0.5	0
	Albumin (Alb)	**G/dL**	609	4.2	0	613	4.2	0
	Aspartate aminotransferase (AST)	**IU/L**	609	23	1	610	22	1
	Alanine aminotransferase (ALT)	**IU/L**	608	24	1	610	23	0
Renal function	**Blood urea nitrogen (BUN)**	**mg/dL**	609	16	0	613	16	0
	Creatinine (Cr)	**mg/dL**	55	1	0	53	1	0
Electrolytes	**Sodium (Na)**	**mEq/L**	609	141	0	613	141	-1
	Potassium (K)	**mEq/L**	607	4.6	-0.1	610	4.6	0
	Chloride (Cl)	**mEq/L**	609	103	1	613	103	0
	Bicarbonate (Bicarb)	**mEq/L**	606	26	-1.4	609	26.4	-1.6
	Calcium (Ca)	**mg/dL**	610	9.5	0	614	9.6	0
	Phosphorus (P)	**mg/dL**	609	3.9	0.1	610	3.9	0.1
Lipids	**Total cholesterol (TC) (random)**	**mg/dL**	590	178.5	1	597	176	0
	Triglycerides (TG) (random)	**mg/dL**	572	68.3	2	575	67.3	1
	Low density lipoprotein (LDL) cholesterol	**mg/dL**	497	103	0	487	102	-1
	High density lipoprotein (HDL) cholesterol	**mg/dL**	578	57	-1	576	57	0
Urinalysis	**Urine white blood cells (Uwbc)**	**cells per high power field**	5	0.5	-0.5	7	1	-1
	Urine red blood cells (Urbc)	**cells per high power field**	30	0	0	31	0	0

Source: Applicant's Table 8.1.1.1, Section 2.7.4

Table 7.1.7.3.1.2 Median Change from Baseline to Last Observation, Safety Laboratory, Adult Type 2 Patients, Phase 2/3 Controlled Trials

			Inh Ins			SQ			OA		
Lab Category	**Lab Test**	**Units**	**N**	**BL Median**	**Median Change from BL**	**N**	**BL Median**	**Median Change from BL**	**N**	**BL Median**	**Median Change from BL**
Heme	**Hb**	**G/dL**	1185	15.3	-0.1	461	15.1	0	572	15.4	-0.1
	Hct	**%**	1126	45	-1	405	45	0	566	46	-1
	RBC	**# x 10^6/mm^3**	882	4.9	-0.1	162	4.9	-0.1	572	4.9	-0.1
	Platelets (Plt)	**# x 10^3/mm^3**	1126	231	3	395	225	-3	565	235	4
	WBC	**# x 10^3/mm^3**	1140	6.5	0	405	6.5	0	572	6.5	0
	Neutrophils	**%**	438	60.1	-0.2	161	60.6	-2	178	61.0	-2.4
	ANC[a]	**# x 10^3/mm^3**	435	3.64	0.04	0			383	3.72	0.11
	Eosinophils	**%**	438	2.7	0.3	161	2.9	0.2	178	2.9	0.5
	Basophils	**%**	438	0.4	0	161	0.4	0	178	0.4	0
	Lymphocytes	**%**	438	29.25	-0.2	161	28.3	1.4	178	28.4	1.2
	Monocytes	**%**	438	6.9	0	161	6.8	0.2	178	6.4	0.1
	MCV	**10^{-15} L**	57	89	0	25	90	0	35	91	0
	MCH	**pG/cell**	497	30	0	25	30	0	424	30	0
	MCHC	**G/dL**	57	34	0	25	34	0	35	34	0
	Bands	**%**	1	2	3	0			0		
LFT	**Total bili**	**mg/dL**	1159	0.4	0	402	0.4	0	619	0.4	0
	Total prot	**G/dL**	460	7.5	0.1	0			425	7.6	0.1
	Alb	**G/dL**	1158	4.2	-0.1	408	4.3	0	612	4.2	0
	AST	**IU/L**	1160	22	1	404	22	1	619	21	1
	ALT	**IU/L**	1160	29	-1	404	29	0	619	30	-1
	Alk Phos	**IU/L**	1155	82	-5	399	83	-3	619	80	-9
Renal	**BUN**	**mg/dL**	1132	17	1	409	18	1	590	17	0
	Cr	**mg/dL**	57	0.9	0	26	0.9	0	36	1	0
Chem	**Na**	**mEq/L**	1158	141	0	409	142	-1	612	140	1
	K	**mEq/L**	1156	4.6	0	402	4.6	-0.1	613	4.5	0
	Cl	**mEq/L**	1158	102	1	409	103.1	0	612	101	1
	Bicarb	**mEq/L**	1156	25.2	-1	406	26	-0.8	609	25	-1
	Ca	**mg/dL**	1146	9.5	0	406	9.6	-0.1	592	9.5	0.1
	P	**mg/dL**	1149	3.7	0.1	402	3.9	0	592	3.7	0.1
Lipids	**TC (random)**	**mg/dL**	705	189	-1	412	188	1	187	193	6
	TG (random)	**mg/dL**	706	143	-13	411	125	4	187	174	7
	LDL	**mg/dL**	1064	112	1	372	110	0	561	118	1
	HDL	**mg/dL**	1131	54	2	402	50	1	590	93	3
Urinalysis	**Uwbc**	**cells/ hpf**	7	1.5	-0.5	1	0.5	-0.5	7	1.5	-1.5
	Urbc	**cells/ hpf**	50	0	0	25	0	0	33	0	0

a Absolute Neutrophil Count
Source: Applicant's Table 8.1.1.2, Section 2.7.4

No significant differences between treatment groups are noted in median change from baseline for these safety laboratory values for either Type 1 or Type 2 diabetics.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

The following tables list numbers of patients who had shifts from a normal baseline to an abnormal value.

Table 7.1.7.3.2.1 Shifts from Normal Baseline to Abnormal Values, Type 1 Diabetics, Controlled Phase 2/3 Studies

				Inh Ins		SQ	
Lab Category	**Lab Test**	**Units**	**Criteria for Abnl**	**Total N**	**n with abn (%)**	**Total N**	**n with abn (%)**
Heme	**Hb**	**G/ dL**	<0.8x BL	620	1 (0.2)	615	0
	Hct	**%**	<0.8x BL	583	1 (0.2)	574	0
	RBC	**10^6/ mm^3**	<0.75 BL	267	1 (0.4)	261	0
	Plt	**10^3/ mm^3**	<75	600	1 (0.2)	600	0
			>700	600	0	600	0
	WBC	**10^3/ mm^3**	<2.5	574	0	572	0
			>17.5	574	0	574	0
	Lymphs	**%**	<0.5x LLN	232	0	240	0
			>1.5x ULN	232	0	240	0
	Neutrophils	**%**	<0.5x LLN	239	0	239	0
			>1.2x ULN	239	0	239	0
	Eosinophils	**%**	>1.5x ULN	225	1 (0.4)	226	1 (0.4)
	Basophils	**%**	>1.0x ULN	249	2 (0.8)	247	0
	Monocytes	**%**	>1.0x ULN	246	3 (1.2)	245	3 (1.2)
	Bands	**%**	>1.0x ULN	10	0	5	1 (20)
	MCV	**10^{-15}/ L**	<0.9x LLN	33	0	33	0
			>1.1x ULN	33	0	33	0
	MCH	**pG/ cell**	<0.9x LLN	32	0	30	0
			>1.1x ULN	32	0	30	0
	MCHC	**G/ dL**	<0.9x LLN	33	0	33	0
			>1.1x ULN	33	0	33	0
LFTs	**Total bili**	**mg/ dL**	>1.5x ULN	593	0	589	3 (0.5)
	AST	**IU/L**	>3x ULN	592	2 (0.3)	595	1 (0.2)
	ALT	**IU/L**	>3x ULN	578	2 (0.3)	582	2 (0.3)
	Alk Phos	**IU/L**	>3x ULN	562	0	573	0
	Albumin	**G/dL**	<0.8x LLN	611	1 (0.2)	617	0
			>1.2x ULN	611	0	617	0
Renal	**BUN**	**mg/ dL**	>1.3x ULN	581	5 (0.9)	583	0
	Cr	**mg/ dL**	>1.3x ULN	572	5 (0.9)	583	0
Lipids	**TC (random)**	**mg/ dL**	>1.3x ULN	443	6 (1.4)	459	2 (0.4)
	TG (random)	**mg/ dL**	>1.3x ULN	560	7 (1.3)	563	4 (0.7)
	HDL	**mg/ dL**	<0.8x LLN	579	1 (0.2)	588	2 (0.3)
	LDL	**mg/ dL**	>1.2x ULN	422	8 (1.9)	440	5 (1.1)
Chem	**Na**	**mEq/ L**	<0.95x LLN	565	0	572	0
			>1.05x ULN	565	0	572	0
	K	**mEq/ L**	<0.9x LLN	581	0	583	0
			>1.1x ULN	581	2 (0.3)	583	2 (0.3)
	Cl	**mEq/ L**	<0.9x LLN	551	0	548	0
			>1.1x ULN	551	0	548	0
	Ca	**mg/ dL**	<0.9x LLN	575	1 (0.2)	581	1 (0.2)
			>1.1x ULN	575	0	581	1 (0.2)
	P	**mg/ dL**	<0.8x LLN	552	2 (0.4)	559	2 (0.4)
			>1.2x ULN	552	3 (0.5)	559	2 (0.4)
	Bicarb	**mEq/ L**	<0.9x LLN	521	5 (1.0)	544	4 (0.7)
			>1.1x ULN	521	5 (1.0)	544	4 (0.7)
UA	**Sp Gr**		<1.001	498	0	493	0
			>1.035	498	22 (4.4)	493	18 (3.7)
	pH		<1.0x LLN	530	0	520	0
			>1.0x ULN	530	0	520	0
	U glu (qual)		≥ 2+	276	54 (19.6)	258	64 (24.8)
	U prot (qual)		≥ 2+	530	1 (0.2)	533	0

Table 7.1.7.3.2.1 Shifts from Normal Baseline to Abnormal Values, Type 1 Diabetics, Controlled Phase 2/3 Studies

				Inh Ins		SQ	
Lab Category	**Lab Test**	**Units**	**Criteria for Abnl**	**Total N**	**n with abn (%)**	**Total N**	**n with abn (%)**
	U WBC	**cells/ hpf**	≥ 6	449	32 (7.6)	435	34 (7.8)
	U RBC	**cells/ hpf**	≥ 6	334	15 (4.5)	327	14 (4.3)
	Ket (qual)		≥ 1+	483	19 (3.9)	471	41 (8.7)
	U bld (qual)		≥ 1+	554	21 (3.8)	560	28 (5.0)
	U bili (qual)		≥ 1+	33	0	35	0

Source: Applicant's Table 8.1.2.1, Section 2.7.4

Table 7.1.7.3.2.2 Shifts from Normal Baseline to Abnormal Values, Type 2 Diabetics, Controlled Phase 2/3 Studies

				Inh Ins		SQ		OA	
Lab Category	**Lab Test**	**Units**	**Criteria for Abnl**	**Total N**	**n with abn (%)**	**Total N**	**n with abn (%)**	**Total N**	**n with abn (%)**
Heme	**Hb**	**G/ dL**	<0.8x BL	1122	4 (0.4)	425	4 (0.9)	553	3 (0.5)
	Hct	**%**	<0.8x BL	1057	2 (0.2)	382	3 (0.8)	532	2 (0.4)
	RBC	**10^6/ mm^3**	<0.75 BL	868	0	159	0	567	0
	Plt	**10^3/ mm^3**	<75	1099	0	379	0	546	0
			>700	1099	0	379	0	546	0
	WBC	**10^3/ mm^3**	<2.5	1105	1 (0.1)	396	1 (0.3)	553	0
			>17.5	1105	1 (0.1)	396	0	553	0
	Lymphs	**%**	<0.5x LLN	432	0	157	0	176	0
			>1.5x ULN	432	0	157	0	176	0
	Neutrophils	**%**	<0.5x LLN	432	0	158	0	178	0
			>1.2x ULN	432	0	158	0	178	0
	Eosinophils	**%**	>1.5x ULN	423	7 (1.7)	145	2 (1.4)	166	6 (3.6)
	Basophils	**%**	>1.0x ULN	446	0	161	0	180	0
	Monocytes	**%**	>1.0x ULN	444	3 (0.7)	160	2 (1.3)	179	2 (1.1)
	Bands	**%**	>1.0x ULN	8	0	5	0	4	0
	MCV	**10^{-15}/ L**	<0.9x LLN	458	0	23	0	396	4 (1.0)
			>1.1x ULN	458	1 (0.2)	23	0	396	0
	MCH	**pG/ cell**	<0.9x LLN	481	2 (0.4)	22	0	413	6 (1.5)
			>1.1x ULN	481	0	22	0	413	0
	MCHC	**G/ dL**	<0.9x LLN	56	0	25	0	33	0
			>1.1x ULN	56	0	25	0	33	0
	ANC		<0.8x LLN	419	9 (2.1)	0	0	370	14 (3.8)
LFTs	**Total bili**	**mg/ dL**	>1.5x ULN	1144	4 (0.3)	399	2 (0.5)	609	1 (0.2)
	AST	**IU/L**	>3x ULN	1115	0	390	0	583	0
	ALT	**IU/L**	>3x ULN	1017	3 (0.3)	370	0	530	0
	Alk Phos	**IU/L**	>3x ULN	1045	0	345	0	554	0
	Total prot	**G/dL**	>1.2x ULN	453	0	0	0	422	0
			<0.8x LLN	453	0	0	0	422	0
	Albumin	**G/dL**	<0.8x LLN	1158	0	406	0	610	0
			>1.2x ULN	1158	0	406	0	610	1 (0.2)
Renal	**BUN**	**mg/ dL**	>1.3x ULN	1057	35 (3.3)	362	5 (1.4)	562	24 (4.3)
	Cr	**mg/ dL**	>1.3x ULN	1116	4 (0.4)	367	0	611	5 (0.8)
Lipids	**TC (random)**	**mg/ dL**	>1.3x ULN	444	2 (0.5)	255	1 (0.4)	107	1 (0.9)
	TG (random)	**mg/ dL**	>1.3x ULN	541	17 (3.1)	331	15 (4.5)	133	9 (6.8)

Table 7.1.7.3.2.2 Shifts from Normal Baseline to Abnormal Values, Type 2 Diabetics, Controlled Phase 2/3 Studies

				Inh Ins		SQ		OA	
Lab Category	**Lab Test**	**Units**	**Criteria for Abnl**	**Total N**	**n with abn (%)**	**Total N**	**n with abn (%)**	**Total N**	**n with abn (%)**
	HDL	**mg/ dL**	<0.8x LLN	1040	10 (1.0)	372	2 (0.5)	544	11 (2.0)
	LDL	**mg/ dL**	>1.2x ULN	810	59 (7.3)	278	15 (5.4)	405	40 (9.9)
Chem	**Na**	**mEq/ L**	<0.95x LLN	1131	1 (0.1)	374	0	606	2 (0.3)
			>1.05x ULN	1131	0	374	0	606	0
	K	**mEq/ L**	<0.9x LLN	1137	1 (0.1)	386	2 (0.5)	603	0
			>1.1x ULN	1137	3 (0.3)	386	3 (0.8)	603	3 (0.5)
	Cl	**mEq/ L**	<0.9x LLN	1100	0	351	0	612	0
			>1.1x ULN	1100	0	351	0	612	0
	Ca	**mg/ dL**	<0.9x LLN	1121	2 (0.2)	378	0	583	1 (0.2)
			>1.1x ULN	1121	0	378	0	583	0
	P	**mg/ dL**	<0.8x LLN	1132	4 (0.4)	372	2 (0.5)	584	0
			>1.2x ULN	1132	1 (0.1)	372	0	584	0
	Bicarb	**mEq/ L**	<0.9x LLN	1083	35 (3.2)	365	6 (1.6)	570	22 (3.9)
			>1.1x ULN	1083	8 (0.7)	365	3 (0.8)	570	1 (0.2)
UA	**Sp Gr**		<1.001	627	0	379	0	167	0
			>1.035	627	6 (1.0)	379	8 (2.1)	167	10 (6.0)
	U pH		<1.0x LLN	1118	0	384	0	590	0
			>1.0x ULN	1118	0	384	3 (0.8)	590	0
	U glu (qual)		≥ 2+	635	29 (4.6)	249	23 (9.2)	351	15 (4.3)
	U prot (qual)		≥ 2+	956	8 (0.8)	326	2 (0.6)	522	1 (0.2)
	U WBC	**cells/ hpf**	≥ 6	673	51 (7.6)	315	31 (9.8)	274	24 (8.8)
	U RBC	**cells/ hpf**	≥ 6	488	17 (3.5)	238	12 (5.0)	235	6 (2.6)
	Ket (qual)		≥ 1+	1042	7 (0.7)	375	5 (1.3)	548	1 (0.2)
	U bld (qual)		≥ 1+	1100	11 (1.0)	388	6 (1.5)	573	7 (1.2)
	U bili (qual)		≥ 1+	57	0	26	0	36	0

1 LLN used by applicant for ANC = 1,700 cells
Source: Applicant's Table 8.1.2.2. Section 2.7.4

Among adult Type 1 and Type 2 patients who had normal laboratory at baseline, the occurrence of glycosuria was common, but did not occur more commonly among inhaled insulin patients than among comparator patients.

The following tables list the incidence of recurrent or worsening laboratory abnormalities among patients who had abnormal laboratory values at baseline.

Table 7.1.7.3.2.3 Incidence of Laboratory Abnormalities Among Adult Type 1 Diabetics with Abnormal Baseline Laboratory[1]

				Inh Ins		SQ	
Lab Category	**Lab Test**	**Units**	**Criteria for Abnl**	**Total N**	**n Meeting both Criteria (%)**	**Total N**	**n Meeting both Criteria (%)**
Heme	**Eosinophils**	**%**	>1.5x ULN and >1.5x BL	25	2 (8.0)	22	1 (4.5)
LFTs	**ALT**	**IU/L**	>3x ULN and >1.5x BL	33	0	33	1 (3.0)
Renal	**BUN**	**mg/ dL**	>1.3x ULN and >1.3x BL	31	1 (3.2)	34	2 (5.9)

Table 7.1.7.3.2.3 Incidence of Laboratory Abnormalities Among Adult Type 1 Diabetics with Abnormal Baseline Laboratory[1]

				Inh Ins		SQ	
Lab Category	**Lab Test**	**Units**	**Criteria for Abnl**	**Total N**	**n Meeting both Criteria (%)**	**Total N**	**n Meeting both Criteria (%)**
Lipids	**TC (random)**	**mg/ dL**	>1.3x ULN and >1.3x BL	152	0	143	1 (0.7)
	TG (random)	**mg/ dL**	>1.3x ULN and >1.5x BL	17	3 (17.6)	17	1 (5.9)
	HDL	**mg/ dL**	<0.8x LLN and <0.8x BL	17	1 (5.9)	12	0
	LDL	**mg/ dL**	>1.2x ULN and >1.2x BL	96	5 (5.2)	73	3 (4.1)
Chem	**Na**	**mEq/ L**	<0.95x LLN and <0.95x BL	47	1 (2.1)	45	0
	P	**mg/ dL**	>1.2x ULN and >1.2x BL	60	0	56	2 (3.6)
UA	**U glu (qual)**		≥ 2+ and >BL+1	315	28 (8.9)	335	39 (11.6)
	U prot (qual)		≥ 2+ and >BL+1	67	1 (1.5)	67	1 (1.5)
	U WBC	**cells/ hpf**	≥ 6 and ≥ 6	20	8 (40)	13	6 (46.2)
	U RBC	**cells/ hpf**	≥ 6 and ≥ 6	28	5 (17.9)	23	8 (34.8)
	Ket (qual)		≥ 1+ and >BL+1	114	2 (1.8)	129	2 (1.6)
	U bld (qual)		≥ 1+ and >BL+1	43	1 (2.3)	40	2 (5.0)

1 Table includes only tests with abnormal values while on study treatment
Source: Applicant's Table 8.1.3.1, Section 2.7.4

Table 7.1.7.3.2.4 Incidence of Laboratory Abnormalities Among Type 2 Diabetics with Abnormal Baseline Laboratory[1]

				Inh Ins		SQ		OA	
Lab Category	**Lab Test**	**Units**	**Criteria for Abnl**	**Total N**	**n Meeting both Criteria (%)**	**Total N**	**n Meeting both Criteria (%)**	**Total N**	**n Meeting both Criteria (%)**
Heme	**Hb**	**G/ dL**	<0.8x LLN and <0.8x BL	75	1 (1.3)	38	0	22	1 (4.5)
	Hct	**%**	<0.8x LLN and <0.8x BL	82	2 (2.4)	29	0	37	1 (2.7)
	RBC	**10^6/ mm^3**	<0.75 LLN and <0.8x BL	25	1 (4.0)	4	0	8	0
	Plt	**10^3/ mm^3**	<75 and <0.8x BL	42	1 (2.4)	25	0	24	0
	WBC	**10^3/ mm^3**	<2.5 and <0.75x BL	46	1 (2.2)	16	0	22	0
	Eosinophils	**%**	>1.5x ULN and >1.5x BL	25	1 (4.0)	17	0	14	2 (14.3)
	MCV	**10^{-15}/ L**	<0.9x LLN and <0.9x BL	36	2 (5.6)	2	0	24	1 (4.2)
	MCH	**pG/ cell**	<0.9x LLN and <0.9x	17	1 (5.9)	3	0	13	1 (7.7)

Table 7.1.7.3.2.4 Incidence of Laboratory Abnormalities Among Type 2 Diabetics with Abnormal Baseline Laboratory[1]

				Inh Ins		SQ		OA	
Lab Category	**Lab Test**	**Units**	**Criteria for Abnl**	**Total N**	**n Meeting both Criteria (%)**	**Total N**	**n Meeting both Criteria (%)**	**Total N**	**n Meeting both Criteria (%)**
			BL						
	ANC		<0.8x LLN[2] and <0.8x BL	17	2 (11.8)	0	0	15	0
LFTs	**AST**	**IU/L**	>3x ULN and >1.5x BL	53	1 (1.9)	17	0	37	0
	ALT	**IU/L**	>3x ULN and >1.5x BL	151	2 (1.3)	37	0	90	1 (1.1)
Renal	**BUN**	**mg/dL**	>1.3x ULN and >1.3x BL	83	6 (7.2)	48	2 (4.2)	29	0
	Cr	**mg/dL**	>1.3x ULN and >1.3x BL	49	2 (4.1)	43	0	2	0
Lipids	**TC (random)**	**mg/dL**	>1.3x ULN and >1.3x BL	264	2 (0.8)	158	0	80	3 (3.8)
	TG (random)	**mg/dL**	>1.3x ULN and >1.5 x BL	168	8 (4.8)	81	9 (11.1)	54	3 (5.6)
	HDL	**mg/dL**	<0.8x LLN and <0.8x BL	123	5 (4.1)	39	0	68	3 (4.4)
	LDL	**mg/dL**	>1.2x ULN and >1.2x BL	318	26 (8.2)	104	7 (6.7)	196	30 (15.3)
Chem	**K**	**mEq/L**	>1.1x ULN and >1.1x BL	27	1 (3.7)	19	0	11	0
	P	**mg/dL**	<0.8x LLN and <0.8x BL	25	0	33	0	8	1 (12.5)
	Bicarb	**mEq/L**	<0.9x LLN and <0.75x BL	83	0	43	1 (2.3)	40	1 (2.5)
UA	**U pH**		>1.0x ULN and >1.0x BL	25	9 (36.0)	23	8 (34.8)	0	0
	U glu (qual)		≥ 2+ and >BL+1	506	13 (2.6)	157	10 (0.64)	239	6 (2.5)
	U prot (qual)		≥ 2+ and >BL+1	184	1 (0.5)	81	0	66	1 (1.5)
	U WBC	**cells/hpf**	≥ 6 and ≥ 6	48	14 (29.2)	14	4 (28.6)	34	5 (14.7)
	U RBC	**cells/hpf**	≥ 6 and ≥ 6	28	7 (25.0)	22	4 (18.2)	2	1 (50.0)
	Ket (qual)		≥ 1+ and >BL+1	101	1 (1.0)	32	0	42	1 (2.4)
	U bld (qual)		≥ 1+ and >BL+1	42	1 (2.4)	19	1 (5.3)	17	1 (5.9)

1 Table includes only tests with abnormal values while on study treatment
2 ANC LLN used by applicant = 1,700 cells
Source: Applicant's Table 8.1.3.2, Section 2.7.4

Baseline glycosuria and lipid abnormalities were common in both Type 1 and Type 2 diabetics in all treatment groups; the development of a worsened degree of glycosuria or hyperlipoproteinemia was not more common among inhaled insulin patients than among comparator patients.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

The applicant did not provide listings or analyses of marked laboratory outliers in the NDA submission. The following table lists marked laboratory outliers among patients taking inhaled insulin in all Phase 2 and Phase 3 trials; these were extracted by the clinical reviewer from the laboratory datasets for all Phase 2/3 trials.

Table 7.1.7.3.3: Marked Laboratory Outliers, Inhaled Insulin Patients, All Phase 2 and Phase 3 Trials

Lab Test	Normal Range and Units	Lab Value	Pt ID	Study Day	Comment
Alanine Aminotransferase, Serum	0-35 U/L	153	1001-0047-3002	372	
		145	1001-0145-1307	736	BL LFTs >3x ULN
		139	1002-0145-6299	636	
		138	1001-0131-2331	127	BL LFTs >3x ULN
Alkaline Phosphatase, Serum	30-120 U/L	614	1009-5079-3380	638	
Bicarbonate, Serum	21-30 mEq/L	40	104-5007-0026	81	
		39	1001-0141-3048	47	
		14.5	1029-1016-0483	374	
		12.8	1029-1110-4985	363	
		11.7	1022-1006-0318	365	
Bilirubin, Serum Total	0.3-1.0 mg/dL	5.7	108-5048-8401	898	
Creatinine, Serum	<1.5 mg/dL	11.5	103-5002-0092	1580	
		5.3	103-5002-0005	2584	
		4.8	108-5072-8386	870	
Eosinophil Count, Absolute	0-1,000 cells	1810	1002-0047-8321	449	
		1630	1002-0141-7398	456	
Gamma Glutamyl Transferase, Serum	1-94 U/L	304	1002-0047-7051	127	
		295	1001-0098-0198	46	Gallstones, fatty liver, permanently discontinued
		265	1001-0145-1307	736	BL LFTs >3x ULN
Glucose, Random Serum	<120 mg/dL	633	106-5064-6517	734	
		514	107-5076-7230	866	

Table 7.1.7.3.3: Marked Laboratory Outliers, Inhaled Insulin Patients, All Phase 2 and Phase 3 Trials

Lab Test	Normal Range and Units	Lab Value	Pt ID	Study Day	Comment
Hemoglobin A1c	3.8-6.4%	15.0	107-5084-7002	1335	
		14.9	106-5064-6519	288	DKA later in study
		14.6	106-5064-6103	352	DKA later in study
		4.3	1027-1016-0646	85	
Neutrophil Count, Absolute	>1,700 cells[2]	1290	1001-0046-1100	205	
		1280	1001-0141-2053	817	
		1280	1001-0002-3301	169	
		1160	1002-0027-6281	184	
		1110	1002-0135-5275	724	
		850	1002-0074-6149	828	
		540	1002-0142-7408	163	Discontinued for severe cough and dyspnea on Study Day 632
		480	1001-0145-1307	169	
Phosphorus, Serum	3-4.5 mg/dL	7.4	103-5002-0092	1599	Renal failure
		6.8	1009-5128-3004	457	
		1.7	1027-5148-1329	86	Occurred on the same day as a severe hypoglycemic episode
		1.5	106-5073-6835	530	
Platelets, Blood	150-350 x $10^3/mm^3$	71K	1029-1096-4029	355	
Potassium, Serum	3.5-5.0 mEq/L	6.4	108-5071-8431	163	
		6.4	1022-1001-0009	106	
		2.9	110-5102-1361	802	
		2.8	103-5006-0047	97	
Red Blood Cells, Urine	0-2/hpf	TNTC	106-5002-6846	894	
		TNTC	107-5041-7152	504	Decline in DLco Study Day 1065
		TNTC	107-5052-7181	533	
		TNTC	107-5061-7798	554	Discontinued same day for declines in FEV1 and DLco
		TNTC	107-5066-7742	707	
		TNTC	108-5007-8550	164	
		TNTC	108-5048-8610	166	Decline in DLco Study Day 344
		TNTC	109-5072-0503	454	
		TNTC	1009-5093-3363	450	
		TNTC	1002-	547	

Table 7.1.7.3.3: Marked Laboratory Outliers, Inhaled Insulin Patients, All Phase 2 and Phase 3 Trials

Lab Test	Normal Range and Units	Lab Value	Pt ID	Study Day	Comment
			0005-6031		
		TNTC	1002-0051-5095	730	
		TNTC	1002-0101-5208	731	
Sodium, Serum	136-145 mEq/L	126	1001-0047-2002	172	
		125	1002-0056-5109	169	
		125	108-5005-8067	729	Discontinued due to bronchitis on Study Day 609 after 435 days inhaled insulin exposure
		122	1022-1008-0448	366	
White Blood Cell Count, Blood	4.5-11.0 x $10^3/mm^3$	1.8	106-5013-6604	526	
		1.7	106-5065-6947	1003	
		1.7	1001-0145-1307	169	

1 Reference ranges from Harrison's Textbook of Internal Medicine, 16th Ed
2 ANC LLN used by applicant
Source: Applicant's datasets allph23/lab11 - allph23/lab19, allph23lab21 - allph23lab29, allph23lab110 - allph23lab123, allph23lab210 - allph23lab218

The clinical reviewer searched for clinical information related to these abnormalities, but most had no narrative or other information in either the individual study report or the overall safety narratives. The clinical reviewer requested further clinical information from the applicant on 16 Jun 05. On 20 Jul 05, the applicant sent, via email, a table which included additional details for some of these patients. For most of these laboratory outliers, there was no report of a recorded event which could have explained the laboratory finding. For those outliers for which a followup value was available, most unexplained abnormal values returned to the normal range.

The one type of laboratory outlier that remained somewhat concerning was low white blood cell count and/or low absolute neutrophil count. However, review of the controlled Phase 2/3 laboratory datasets revealed that similar percentages of control patients also exhibited outlier values in these ranges for white blood cell count and absolute neutrophil count (Source: crt/datasets/CNTPH23lab12 and crt/datasets/CNTPH23lab 213).

Discontinuations due to laboratory abnormalities were discussed in Section 7.1.3.

7.1.7.4 Additional analyses and explorations

Because there were no significant differences between inhaled insulin groups and comparator groups for laboratory abnormalities in controlled Phase 2/3 trials, explorations for dose dependency, time dependency, drug-demographic interactions, drug-disease interactions, and drug-drug interactions were not applicable.

7.1.7.5 Special assessments

7.1.7.5.1 Hepatotoxicity

Transaminase elevations did not occur at a higher rate among inhaled insulin patients than among comparator patients in the controlled Phase 2/3 study population. Additional information was requested from the applicant on 16 Jun 05 regarding patient 108-5048-8401, who had an elevated bilirubin of 5.7 mg/dL on day 898, per the applicant's laboratory datasets for all Phase 2 and Phase 3 studies. The laboratory outlier table sent by the applicant on 20 Jul 05 reported that no event was recorded to coincide with this bilirubin value. However, the patient had a baseline bilirubin of 4.7 mg/dL, and his bilirubin on day 911 was 5.1 mg/dL. It appears that this patient had baseline hyperbilirubinemia that was not substantially worsened after inhaled insulin exposure. Additional information was requested from the applicant on 16 Jun 05 regarding patient 104E-5011-0034, who had a serious adverse event of jaundice and increased liver function tests. On 18 Jul 05, Mr. Brian Green sent a narrative regarding this patient via email. This 69 year old man had negative hepatitis serology, and was suspected to have a drug-induced hepatitis related to irbesartan. Discontinuation of irbesartan was followed by resolution of jaundice, but LFTs remained elevated. Several months later, the patient had a 7 mm biliary stone removed via endoscopic retrograde cholangiopancreatography. The applicant did not have data regarding resolution of the elevated LFTs. Overall, there does not appear to be a signal of hepatotoxicity for Exubera®.

7.1.7.5.2 QTc

An intensive QTc study was not performed. Electrocardiograms were performed at baseline in Phase 2 and Phase 3 studies, but routine electrocardiograms (ECGs) were not performed after baseline in Studies 1001, 1002, 102, 1026, 1027, and 1029. ECGs were not performed at specific times relative to study drug administration. From routine electrocardiograms from those studies for which postbaseline ECGs were obtained, mean changes in QTc were not significantly different between inhaled insulin and comparator patients in controlled Phase 2 and Phase 3 studies. Bazzett's correction was used for QTc.

Table 7.1.7.5.2.1 Mean Changes in QTc, Adult Population, Controlled Phase 2 and Phase 3 Studies

	Type 1 Patients		Type 2 Patients		
	Inh Ins n = 252	**SQ n = 248**	**Inh Ins n = 907**	**SQ n = 167**	**OA n = 579**
QTc BL msec (SD)	408.8 (30.8)	407.8 (24.2)	411.8 (41.6)	415.1 (24.2)	409.9 (45.8)
QTc Mean Δ from BL msec (SD)	-6.0 (30.8)	-1.0 (21.2)	1.0 (27.3)	1.0 (23.6)	2.0 (30.5)

Source: Applicant's Tables 10.1.2.2 and 10.1.2.1, ISS

From routine electrocardiograms, outlier abnormalities of the QTc interval did not occur more frequently among inhaled insulin patients than among comparator patients in controlled Phase 2 and Phase 3 studies, as illustrated in the following table.

Table 7.1.7.5.2.2 QTc Changes from Baseline with Outliers, Adult Patients, Controlled Phase 2 and Phase 3 Studies

	Type 1 Patients		Type 2 Patients		
QTc Change from Baseline	**Inh Ins (n = 251) n (%)**	**SQ n = 247 n (%)**	**Inh Ins n = 898 n (%)**	**SQ n = 167 n (%)**	**OA n = 573 n (%)**
≤ 30 msec	233 (92.8)	232 (93.9)	846 (94.2)	153	552
>30 to ≤ 60 msec	15 (6.0)	14 (5.7)	44 (4.9)	11 (6.6)	16 (2.8)
>60 msec	3 (1.2)	1 (0.4)	8 (0.9)	3 (1.8)	5 (0.9)

Source: Applicant's Tables 80 and 81, ISS 2.7.4 Section 4.4

There was no difference between groups in frequency of QTc outliers by gender (source Applicant's Tables 10.1.4.1 and 10.1.4.2, ISS).

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs (systolic and diastolic blood pressure, pulse) were measured at baseline and at end of study or time of study discontinuation. Body weight was a secondary endpoint in some studies, but is presented here because of its occurrence as an undesirable association with improved or intensive glycemic control.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The clinical reviewer used the controlled Phase 2 and Phase 3 populations for comparisons of frequencies of vital signs abnormalities.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Mean pulse and blood pressure did not change substantially from baseline to last observation for adults patients, and there were no significant differences between treatment groups.

Table 7.1.8.3.1.1 Mean Change from Baseline in Pulse and Blood Pressure, Adult Patients, Controlled Phase 2 and Phase 3 Studies

	Type 1		Type 2		
	Inh Ins n = 684 Mean Δ (SD)	SQ n = 687 Mean Δ (SD)	Inh Ins n = 1,243 Mean Δ (SD)	SQ n = 481 Mean Δ (SD)	OA n = 599 Mean Δ (SD)
Systolic BP (mmHg)	0.98 (13.61)	0.41 (13.50)	-1.11 (16.77)	0.53 (16.09)	-3.15 (18.29)
Diastolic BP (mmHg)	-0.15 (9.09)	-0.06 (9.21)	-1.18 (9.51)	0.05 (9.60)	-2.18 (9.90)
Pulse (bpm)	0.31 (10.48)	-0.33 (10.04)	0.09 (10.05)	-0.45 (10.24)	0.09 (9.95)
Source: Applicant's Tables 9.1.1.1 and 9.1.1.2, ISS					

Among adult Type 1 diabetics in Studies 106 and 107, there was little difference between treatment groups for mean change in body weight.

Table 7.1.8.3.1.2 Mean Change from Baseline in Body Weight (kg), Adult Type 1 Patients, Studies 106 and 107, ITT Population

Study	Tx Grp	N	BL (SD)	EOS (SD)	Mean Δ (SD)	Adj Diff (95% CI)
106	Inh Ins	135	77.4 (14.9)	77.7 (14.9)	0.3 (3.1)	-0.72 (-1.48, 0.04)
	SQ	134	76.4 (13.0)	77.4 (13.7)	1.0 (3.2)	
107	Inh Ins	103	76.0 (13.6)	76.5 (14.3)	0.5 (3.5)	-0.24 (-1.07, 0.59)
	SQ	104	76.9 (14.1)	77.7 (14.7)	0.7 (2.5)	
Source: Applicant's Tables 1.7.1.1, 1.7.1.2, Section 2.7.3						

Type 2 patients who were insulin-using at study entry did not gain more weight with inhaled insulin than with comparator; in Study 108, SQ patients actually gained statistically significantly more weight (1.28 kg, 95% CI 0.6-1.96). However, inhaled insulin patients who were not using insulin at study entry did have statistically significantly greater weight gain than comparator patients in several studies, as illustrated in the following table.

Table 7.1.8.3.1.3 Mean Change from Baseline in Body Weight (kg), Type 2 Patients, Non-insulin-using at Study Entry, Controlled Phase 2 and Phase 3 ITT Populations

Study	Tx Grp	N	BL (SD)	EOS (SD)	Mean Δ (SD)	Adj Diff (95% CI)
109	Inh Ins	103	89.5 (15.8)	92.3 (15.2)	2.8 (3.6)	2.80 (1.94, 3.65)[a]
	Inh Ins + OA	101	88.6 (15.5)	91.3 (16.6)	2.7 (3.3)	2.75 (1.89, 3.61)[b]
	OA	96	88.0 (15.4)	88.0 (15.5)	-0.1 (1.9)	
110	Inh Ins	75	92.9 (17.6)	94.8 (16.1)	1.9 (3.7)	0.95 (-0.18, 2.09)
	Rosi	68	93.1 (23.9)	93.9 (23.3)	0.8 (3.7)	
1001 (6 month data, pts with BL HbA1c 8-9.5%)	Inh Ins + SU	102	79.9 (12.3)	82.3 (12.5)	2.3 (2.8)	2.67 (1.84, 3.51)
	Met + SU	93	81.9 (14.0)	81.6 (14.0)	-0.3 (2.4)	
1001 (6 month data, pts with BL HbA1c >9.5-12%)	Inh Ins + SU	112	80.8 (14.6)	84.4 (15.2)	3.5 (3.7)	3.60 (2.81, 4.39)
	Met + SU	103	79.5 (14.6)	79.4 (14.9)	0 (2.6)	
1002 (6 month data, pts with BL HbA1c 8-9.5%)	Inh Ins + Met	123	90.3 (16.6)	92.2 (16.9)	1.8 (3.7)	0.38 (-0.52, 1.27)
	Gli[c] + Met	114	88.2 (16.5)	89.7 (16.7)	1.5 (2.9)	
1002 (6 month data, pts with BL HbA1c >9.5-12%)	Inh + Met	105	88.3 (17.0)	90.9 (16.9)	2.6 (3.5)	0.26 (-0.70, 1.21)
	Gli + Met	102	87.8 (16.3)	90.2 (16.9)	2.4 (3.8)	

a Comparison of Inh Ins to OA
b Comparison of Inh Ins+OA to OA
c Glibenclamide
Source: Applicant's Table 26, Section 2.7.3.3.2.2.5

The difference in weight gain was most evident in Study 1001, in which add-on inhaled insulin was compared to add-on metformin.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

The applicant did not submit analyses of vital signs data for shifts from normal to abnormal.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

The applicant did not submit outlier analyses for vital signs data.

There was no significant difference between treatment groups in the frequency of adverse events of hypotension and hypertension, as illustrated in the following table.

Table 7.1.8.3.3.1 Adverse Events of Hypotension and Hypertension, Adult Patients, Controlled Phase 2 and Phase 3 Studies

	Type 1		Type 2		
	Inh Ins n = 698 n (%)	**SQ n = 705 n (%)**	**Inh Ins n = 1,277 n (%)**	**SQ n = 488 n (%)**	**OA n = 644 n (%)**
Hypotension	0	0	4 (0.3)	0	0
Hypertension	20 (2.9)	14 (2.0)	106 (8.3)	39 (8.0)	49 (7.6)
Source: Applicant's Table 68, Section 2.1.5.3.1					

No inhaled insulin group patients were reported to have discontinued due to a change in blood pressure or pulse.

The following table lists patients identified by investigators as having had significant change in body weight. The definition for the applicant's criterion for a significant change in weight was not noted. For Type 2 patients, investigators reported more events of significant weight gain among inhaled insulin patients than among comparator patients.

Table 7.1.8.3.3.2 Adult Patients with Significant Changes in Body Weight, Controlled Phase 2 and Phase 3 Studies

Tx Grp	DM Type	Pt ID	Amt of Wt Incr (kg)[2]
Inh Ins	1	106-5051-6277	11.8
SQ	1	1022-5060-2907	NV[1]
	1	1027-1005-0208	4.5
Inh Ins	2	1001-0018-0059	5
	2	1001-0018-1057	8
	2	1001-0018-1058	6-8
	2	1001-0045-0093	6.5
	2	1001-0045-3362	5
	2	1001-0065-0157	NV
	2	1002-0045-5079	NV
	2	109-5026-0602	11.4
	2	109-5127-0161	NV
	2	110-5058-1409	NV
	2	110-5112-1371	NV
OA (glibenclamide)	2	1002-0141-8034	NV

1 No value given
2 Amount of weight gain from patient's adverse event report
Source: Applicant's Table 9.1.3.1 and 9.1.3.2, Section 2.7.4

Only one patient in all phase 2 and Phase 3 trials discontinued treatment due to weight gain, patient 1029-1033-2138, a 53 year old Type 2 diabetic woman who discontinued after 60 days on inhaled insulin treatment. Her measured weight gain was negligible, with a weight on Study Day 1 of 83.4 kg, on Study Day 30 of 84.1 kg, and on Study Day 58 of 83.6 kg.

7.1.8.4 Additional analyses and explorations

As there were few differences between treatment groups for blood pressure and pulse, additional analyses were not performed for dose dependency, time dependency, drug-demographic interactions, drug-disease interactions or drug-drug interactions.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Electrocardiograms were performed at baseline in Phase 2 and Phase 3 studies, but they were not performed routinely after baseline in Studies 1001, 1002, 1022, 1026, 1027 and 1029. ECGs

were not performed at a specific time relative to study drug administration. QTc is discussed above in Section 7.1.7.5.2.

Pharmacologic toxicology review of preclinical data related to cardiac conduction is ongoing as of 6 Jul 05.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The controlled Phase 2 and Phase 2 studies for which ECGs were routinely performed at baseline and at least once after baseline were used for comparisons.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Among Adult Type 1 and Type 2 diabetics, there was little difference between groups for mean changes in heart rate, PR interval or QRS width.

Table 7.1.9.3.1.1 Mean Changes in ECG Parameters, Adult Type 1 Diabetics, Controlled Phase 2 and Phase 3 Studies with ECGs at Baseline and at Least Once After Baseline

Parameter (units)	Inh Ins n = 252 Mean BL (SD)	SQ n = 248 Mean BL (SD)	Inh Ins n = 252 Mean Change from BL to Last Observ (SD)	SQ n = 248 Mean Change from BL to Last Observ (SD)
Heart rate (bpm)	69.0 (11.0)	69.9 (11.4)	0 (9.6)	0 (9.2)
PR Interval (msec)	148.6 (23.8)	150.6 (22.0)	2.0 (18.2)	1.0 (13.9)
QRS Width (msec)	85.0 (12.5)	84.1 (12.8)	0 (8.4)	0 (10.3)
Source: Applicant's Table 10.1.2.1, Section 2.7.4				

Table 7.1.9.3.1.2 Mean Changes in ECG Parameters, Type 2 Diabetics, Controlled Phase 2 and Phase 3 Studies with ECGs at Baseline and at Least Once After Baseline

Parameter (units)	Inh Ins n = 907 Mean BL (SD)	SQ n = 167 Mean BL (SD)	OA n = 579 Mean BL (SD)	Inh Ins n = 907 Mean Change from BL to Last Observ (SD)	SQ n = 167 Mean Change from BL to Last Observ (SD)	OA n = 579 Mean Change from BL to Last Observ (SD)
Heart rate (bpm)	72.3 (11.7)	72.2 (11.4)	74.0 (12.1)	1.0 (10)	0 (10.2)	0 (10.4)
PR Interval (msec)	163.4 (27.1)	159.1 (26.8)	161.9 (26.3)	1.0 (17.8)	0 (13.9)	3.0 (15.4)
QRS Width (msec)	88.6 (17.6)	87.9 (14.7)	87.6 (17.6)	1.0 (11.1)	1.0 (10.5)	1.0 (8.6)
Source: Applicant's Table 10.1.2.2, Section 2.7.4						

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

The applicant did not submit analyses of shifts from abnormal to abnormal for ECG data.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

The applicant did not submit analyses of ECG outliers.

One Type 2 diabetic inhaled insulin group patient, a 64 year old man (ID 103-5014-0022), discontinued treatment on Study Day 84 due to a cerebrovascular accident, bradycardia and premature ventricular contractions that had begun on Study Day 82.

7.1.9.4 Additional analyses and explorations

Because no significant differences were noted between treatment groups for ECG abnormalities, additional explorations were not performed for dose dependency, time dependency, drug-demographic interactions, drug-disease interactions or drug-drug interactions.

7.1.10 Immunogenicity

Please see Section 7.1.3.3.2 for a discussions of the development of insulin antibodies among inhaled insulin patients, and the occurrence of allergic and immune events.

The actual drug substance used did not exhibit inherent immunogenicity in in which 476 insulin-naïve Type 2 patients were randomized to receive either for one year. Rates of insulin antibody development did not differ between groups.

7.1.11 Human Carcinogenicity

Malignant neoplastic adverse events in humans are discussed in Sections 7.1.2.1, 7.1.3.2 and 7.1.6. Overall, malignant neoplasms did not occur at a higher frequency in inhaled insulin patients than in comparator patients for either Type 1 or Type 2 diabetics. In controlled Phase 2 and Phase 3 trials in Type 2 diabetics, discontinuations due to neoplasia did not occur more frequently among inhaled insulin group patients than among control patients. One case of lung carcinoma occurred in the inhaled insulin groups, and one in the oral agent groups. Pulmonary neoplasms are to be discussed in Dr. Seymour's pulmonary safety review. For all Phase 2 and Phase 3 trials, controlled and uncontrolled, neoplastic adverse event terms leading to discontinuation were numerically more frequent and slightly (not statistically significantly) more frequent on a person-time basis in the inhaled insulin groups than in the control groups.

The applicant did not conduct animal carcinogenicity studies with inhaled insulin.

7.1.12 Special Safety Studies

Dr. Seymour's pulmonary safety review will include discussion of specific pulmonary safety studies; please see Section 7.1.3.3 for a discussion of insulin antibody studies.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The abuse potential of inhaled insulin was not evaluated by the applicant. Recreational abuse of insulin is unlikely, as it is not known to induce pleasurable effects generally associated with drugs of abuse. One accidental overdose of inhaled insulin occurred during the drug development program, resulting in hypoglycemia, but no unexpected adverse effects.

Studies 111, 1001, 1002, and 1027 included withdrawal of inhaled insulin, and substitution of subcutaneous insulin as subsequent insulin treatment. An increased incidence of hypoglycemia was noted during the initial period of replacement with subcutaneous insulin. Withdrawal of inhaled insulin was associated with increases (returns toward baseline) in FEV1 and DLco compared to inhaled insulin continuation. Withdrawal of inhaled insulin was associated with decreases (returns toward baseline) in insulin antibody levels. No withdrawal phenomena suggestive of addictive potential were reported.

Inhaled insulin does not appear to have abuse potential, but withdrawal of inhaled insulin requires an initial period of increased monitoring and careful medical supervision, with vigilance for hypoglycemia, as subcutaneous therapy is instituted.

7.1.14 Human Reproduction and Pregnancy Data

The applicant did not conduct animal reproduction studies with Exubera®.

Study 1007 was a clinical pharmacokinetic and pharmacodynamic study conducted in 10 gestational and 3 pregestational diabetic women. It was an open-label, randomized, two-period, two-treatment, crossover study. Each subject received a single morning fasting dose of either 9 U regular SQ insulin or 1 puff of 3 mg inhaled insulin, then no study insulin for 14 days (with continued usual management of their diabetes), then a single dose of cross-over study medication.

Insulin Tmax was earlier with inhaled insulin administration than with regular SQ insulin. Cmax was 83% higher with inhaled insulin than with regular SQ. AUC_{0-360} was similar for both treatments.

Table 7.1.14.1 Insulin Pharmacokinetics, Study 1007, Gestational and Pregestational Pregnant Diabetics

	Inh Ins mean (SD)	SQ mean (SD)	Ratio or Difference	95% CI for Diff Between Grps
AUC_{0-360} (µU-min/mL)	2435 (50)	2630 (57)	93%	55%, 155%
Cmax (µU/mL)	39.0 (57)	21.3 (57)	183%	116%, 290%

Table 7.1.14.1 Insulin Pharmacokinetics, Study 1007, Gestational and Pregestational Pregnant Diabetics				
	Inh Ins mean (SD)	**SQ mean (SD)**	**Ratio or Difference**	**95% CI for Diff Between Grps**
Tmax (min)	45.8 (39)	82.9 (63)	-37.1 min	-75.1 min, 1.0 min
Source: Applicant's Tables 5.2.1, 5.2.2, 5.3.1, Study 1007 report				

Insulin Tmax in this study was similar to that seen in nonpregnant diabetics in other studies, where Tmax ranged from 38-78 minutes. Fasting insulin Cmax in these women was also similar to fasting insulin Cmax seen in nonpregnant diabetics. Bioavailability of inhaled insulin relative to SQ was 10% based on geometric mean; this relative bioavailability is similar to that seen in nonpregnant women.

Mean maximum reduction of plasma glucose was similar between treatments; time to maximum reduction of glucose was numerically, although not statistically significantly, shorter with inhaled insulin than with regular insulin. The lack of statistical significance of the difference in time to maximum reduction of glucose may have been due to small sample size.

Table 7.1.14.2 Glucose Pharmacodynamics, Study 1007, Gestational and Pregestational Pregnant Diabetics				
	Inh Ins mean (SD)	**SQ mean (SD)**	**Ratio or Difference**	**95% CI for Diff Between Grps**
AUC_{0-360} (µU-min/mL)	6083 (41)	5582 (50)	109%	80%, 148%
Maximum decline in glu conc (mg/dL)	28.8 (35)	28.1 (44)	103%	81%, 130%
Time to maximum decline in glu conc (min)	210 (62)	275 (24)	-65.0 mg/dL	-142.3 mg/dL, 12.3 mg/dL
Source: Applicant's Tables 5.4, 5.5.1, Study 1007 report				

Time to maximum decline in glucose was somewhat shorter for pregnant inhaled insulin patients in this study (210 minutes) than for nonpregnant Type 2 diabetics receiving inhaled insulin in Study 1004, where the time to maximum decline in glucose was 248 minutes. The maximum decline in glucose concentration was less in these pregnant diabetics exposed to inhaled insulin than it was in nonpregnant Type 2 diabetics in Study 1004, but significant differences in baseline glucose levels and patient age limit the interpretability of this observation.

One subject was discontinued from Study 1007 after completing her first treatment (inhaled insulin). Discontinuation was due to a prolapsed umbilical cord, resulting in a Caesarian delivery. Two women had hypoglycemic episodes two hours after administration of inhaled insulin; no women became hypoglycemic after SQ insulin administration. Pregnancy outcomes were not reported.

In other studies in the clinical development program, a total of 10 women became pregnant while taking inhaled insulin, and two women became pregnant while taking SQ insulin. All patients were discontinued from study once their pregnancy was reported. The following table lists these patients and their pregnancy outcomes.

Table 7.1.14.3 Pregnancy Occurrence and Outcome, All Phase 2 and Phase 3 Studies

Patient	Trtmnt	Age	DM Type	Time on Treatment (days) Prior to DC	EGA at Time of Last Study Drug Dose	Last Known Insulin Antibody Level	Last Known HbA1c	Pregnancy Outcome
111-5059-6684	Inh Ins	29	1	243	1-2 months	14% binding	8.4%	No narrative; reported uncomplicated Caesarian delivery
111-5029-8422	Inh Ins	37	2	209	4 wks	21% binding	7.9%	No narrative; reported sp abortion at appr 14 wks after LMP, abnl fetal karyotype
111-5007-7988	Inh Ins	22	1	916	Unk	23% binding	9.2%	No narrative re pregnancy; reported sp abortion at unk gest age, 7 weeks after DC of inh ins. Pt also had recurrent severe hypoglycemia and decline in DLco
102E-5007-0073	Inh Ins	31	1	207	6 wks	Not measured	8.9%	No narrative; healthy birth by C-section at 36 weeks EGA
1022-1006-0305	Inh Ins	27	1	42	2 mos	24 µU/mL	7.8%	No narrative; reported deliv near term
106-5016-6932	Inh Ins	28	1	53	Unk	<3% binding	5.5%	Unk; subject moved out of state; no narrative
1022-1039-2253	Inh Ins	21	1	110	11 wks	20 µU/mL	9.2%	Preterm labor at 31 wks EGA; C-section at 32 weeks EGA. Neonatal cardiomegaly and macrosomia; neonatal death at age 2 days. See Section 7.1.1 (deaths) for further details
1022-1047-2730	Inh Ins	27	1	176	Unk	89 µU/mL	9.0%	Sp abortion shortly after becoming pregnant; no narrative
1022-5155-3735	Inh Ins	42	1	304	5 weeks	185 µU/mL	7.2%	Sp abortion at 10 wks EGA; no narrative
1027-1015-0600	Inh Ins	31	1	86	3 mos	31 µU/mL	5.6%	Healthy birth near term. Neonatal hypoglycemia one hour after delivery. No narrative
1022-1008-0447	SQ	29	1	SQ cont	SQ cont	4.6 µU/mL	6.9%	Birth at 37 wks EGA; LGA and neonatal hypoglycemia, Apgars 6 and 9. No narrative.
1022-1023-1306	SQ	20	1	SQ cont	SQ cont	<2 µU/mL	6.2%	Pregnancy ongoing at time of reporting; no complications. No narrative.

Source: Applicant's Table 87, ISS

The applicant did not provide narratives for most of these pregnancies. The case of neonatal death is discussed further in the Deaths section (7.1.1). Transient neonatal hypoglycemia occurred in one patient exposed to inhaled insulin; this is a common event in infants of diabetics mothers in general.

Clinically apparent spontaneous abortions occur in insulin-requiring diabetic women at a rate roughly twice that of the normal population of pregnant women (29.5% vs 10-15%) (Miodovnik 1988). In the Exubera® development program, 4/10 women who became pregnant while taking inhaled insulin had a spontaneous abortion. The risk for spontaneous abortion in pregnant Type 1 diabetics is increased with poor glycemic control in the first trimester; however, the threshold for increased risk occurs with initial HbA1c concentrations above 12% (Rosenn 1994). None of the inhaled insulin patients who had spontaneous abortions had HbA1cs >12%, although two had HbA1cs ≥ 9%.

In Studies 106 and 107, mean end-of-study insulin antibody levels for Type 1 nonpregnant diabetic women were 32.6% binding (SD 22.46) for the semiquantitative Mayo assay, and 435.0 µU/mL (SD 1194.2) for the quantitative Esoterix® assay. None of the women in the development program who had adverse pregnancy outcomes had known insulin antibody levels higher than these means.

The applicant proposes Pregnancy Category C for Exubera®, with the following language for the label:

"Animal reproduction studies have not been conducted with EXUBERA. It is also not known whether EXUBERA can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. EXUBERA should be given to a pregnant woman only if clearly needed."

The information obtained about human reproductive risk of Exubera® is not substantial enough at this time to conclude that Exubera® can cause fetal harm, and thus Pregnancy Categories D or X are not warranted. However, some information is available in pregnant women which could assist clinicians in decision-making about whether or not to choose Exubera® for the treatment of pregnant women. The clinical reviewer recommends the addition to the label of a summary of the known information about the pregnancy outcomes of women exposed to Exubera®.

7.1.15 Assessment of Effect on Growth

In Study 1009, conducted in children ages 6-11 years, height was not reported after baseline, and no datasets were provided. In Studies 106 and 107, which included adolescents ages 12-18, height was not reported after baseline, and datasets did not include height data. The applicant's Table 4.2.1.1.1.1 lists one case of growth retardation among Type 1 diabetics exposed to inhaled insulin in all Phase 2 and Phase 3 studies, but no patient identification number was included to permit review of this case. Data are insufficient for conclusions regarding the potential effect of Exubera® on growth.

7.1.16 Overdose Experience

One accidental overdose of inhaled insulin occurred during the drug development program, resulting in hypoglycemia, but no unexpected adverse effects.

7.1.17 Postmarketing Experience

Not applicable.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

An enormous volume of information was submitted for review with the Exubera® application. The original NDA, submitted 27 Dec 04, contained 17.9 GB of information, 17 of which were clinical. Between 28 Dec 04 and 20 Jun 05, the applicant submitted an additional 0.7 GB of information. One GB of electronic information is roughly equivalent to 100,000 pages of text information.

Safety data from all Phase 2 and Phase 3 studies were used in the safety evaluation. Information for comparison of rates of safety findings was obtained from the controlled Phase 2 and Phase 3 study data. The applicant provided, in electronic form, overall safety summary information, reports of all completed Phase 2 and Phase 3 studies, and partial reports of some ongoing studies. Datasets were provided for some, but not all, individual studies. An overall safety database was provided for the controlled Phase 2 and Phase 3 studies, including both inhaled insulin and comparator data. A separate database was provided for the population of inhaled insulin patients exposed in all Phase 2 and Phase 3 studies, both controlled and uncontrolled. This database did not include comparator patient data. Narratives or case report forms were provided only for deaths, serious adverse events that the applicant felt were study-drug-related, adverse events which led to discontinuation, and pulmonary adverse events.

7.2.1.1 Study type and design/patient enumeration

Please see Section 4.2 for a tabular summary of the type and design of clinical studies.

The cut-off date for routine safety data for the NDA was 25 Jun 04; the cut-off date for serious adverse event data was 1 Sep 04.

As of 25 Jun 04, a total of 3,603 patients had been exposed to inhaled insulin. Of these, 3,272 were adults, and 331 were <18 years old. For the 4-month safety update (cut-off 13 Dec 04), data for only two additional patients were submitted; both patients were exposed to inhaled insulin. The following table details overall exposure by patient number:

Table 7.2.1.1.1 Overall Exposure to Inhaled Insulin by Numbers of Patients, Data Cut-off 25 Jun 04

Study Type	Subject Type	Inh Ins	SQ	OA	Total
Clin Pharm	Nondiabetic	696	493	0	699
	Diabetic	125	123	0	127
	All Clin Pharm	821	616	0	826

Table 7.2.1.1.1 Overall Exposure to Inhaled Insulin by Numbers of Patients, Data Cut-off 25 Jun 04

Study Type	Subject Type	Inh Ins	SQ	OA	Total
Controlled Phase 2/3 Studies	Type 1 Diabetics	851	853	0	1,704
	Type 2 Diabetics	1,277	1,341	644	4,113
	All Contr Ph 2/3	2,128	1,365	644	4,133
All Phase 2/3 Studies	Type 1 Diabetics	1,209	869	0	1,714
	Type 2 Diabetics	1,578	496	648	2,419
	All Pts, Ph 2/3	2,787	1,365	648	4,133
All Studies	**All Subjects, All Studies**	**3,603**	**1,981**	**648**	**4,959**

Source: Applicant's Table 1.1.1, ISS Appendix

The following table presents pediatric exposure by numbers of patients. No Type 2 diabetic children were studied.

Table 7.2.1.1.2 Exposure for Patients <18 Years of Age, Data Cut-off 25 Jun 04

Study Type	Subject Type	Inh Ins	SQ	Total
Clin Pharm	Nondiabetic	20	20	20
	Type 1 Diabetic	25	26	27
	All Phase 1	45	46	47
Controlled Phase 2/3	Type 1 Diabetic	153	148	301
All Ph 2/3	Type 1 Diabetic	291	148	301
All Studies	**All Children, All Studies**	**331**	**194**	**348**

Source: Applicant's Table 1.1.2, Section 2.7.4

In the controlled Phase 2/3 studies in adults, a total of 214 Type 1 and 375 Type 2 diabetic patients were exposed to inhaled insulin for more than 12 months. The following table presents adult exposure in the controlled Phase 2/3 population.

Table 7.2.1.1.3 Exposure by Duration, Controlled Phase 2/3 Studies in Adults, Cut-off 25 Jun 04

	Type 1		Type 2		
Exposure (months)[1]	**Inh Ins n = 698 n (% of tx grp)**	**SQ n = 705 n (% of tx grp)**	**Inh Ins n = 1,277 n (% of tx grp)**	**SQ n = 488 n (% of tx grp)**	**OA n = 644 n (% of tx grp)**
>0-3	159 922.8)	165 (23.4)	365 (28.6)	45 (9.2)	209 (32.5)
>3-6	264 (37.8)	249 (35.3)	288 (22.6)	141 (28.9)	137 (21.3)
>6-12	61 (8.7)	64 (9.1)	249 (19.5)	121 (24.8)	99 (15.4)
>12-18	158 (22.6)	169 (24.0)	183 (14.3)	148 (30.3)	48 (7.5)
>18-24	56 (8.0)	58 (8.2)	136 (10.6)	33 (6.8)	107 (16.6)
>24-30	0	0	56 (4.4)	0	44 (6.8)
Median Exposure (months)	5.59	5.65	5.88	9.71	5.60
Overall Exposure (patient-months)	**5,894**	**6,052**	**12,187**	**4,868**	**6,453**

1 Numbers not cumulative; patients counted only once in their final treatment duration category
Source: Applicant's ISS Appendix Tables 2.1.1.1, 2.1.1.2

Median exposure among inhaled insulin patients in all Phase 2 and Phase 3 trials was considerably longer than that seen in the controlled Phase 2/3 trial population (15.34 vs 5.59 for Type 1, 17.49 vs 9.71 for Type 2). A total of 585 Type 1 and 996 Type 2 patients had exposure of at least 12 months, with some patients exposed for as long as 7 years.

The following table presents duration of exposure by ranges of exposure, and cumulative exposure for adult patients in all Phase 2 and Phase 3 studies.

Table 7.2.1.1.4 Duration of Exposure, All Phase 2 and Phase 3 Studies, Inhaled Insulin Patients, Data Cut-off 25 Jun 04

	Type 1 n = 918	Type 2 n = 1,578		Type 1 n = 918	Type 2 n = 1,578
Exposure (months)[1]	**n (%)**	**n (%)**	**Cumulative Exposure (months)[2]**	**n (%)**	**n (%)**
>0-3	144 (15.7)	114 (7.2)	>0	918 (100)	1,578 (100.0)
>3-6	90 (9.8)	171 (10.8)	>3	774 (84.3)	1,464 (92.8)
>6-12	99 (10.8)	297 (18.8)	>6	684 (74.5)	1,293 (81.9)
>12-18	195 (21.2)	250 (15.8)	>12	390 (42.5)	746 (47.3)
>18-24	144 (15.7)	244 (15.3)	>24	246 (26.8)	502 (31.8)
>24-30	115 (12.5)	241 (15.3)	>24	246 (26.8)	502 (31.8)
>30-36	83 (9.0)	156 (9.9)	>30	131 (14.3)	261 (6.7)
>36-42	17 (1.9)	45 (2.9)	>36	48 (5.2)	105 (6.7)
>42-48	1 (0.1)	5 (0.3)	>42	31 (3.4)	60 (3.8)
>48-54	1 (0.1)	4 (0.3)	>48	30 (3.3)	55 (3.5)
>54-60	3 (0.3)	3 (0.2)	>54	29 (3.2)	51 (3.2)
>60-66	2 (0.2)	5 (0.3)	>60	26 (2.8)	48 (3.0)
>66-72	0	16 (1.0)	>66	24 (2.6)	43 (2.7)
>72-78	1 (0.1)	14 (0.9)	>72	24 (2.6)	27 (1.7)
>78-84	15 (1.6)	8 (0.5)	>78	23 (2.5)	13 (0.8)
>84	8 (0.9)	5 (0.3)	>84	8 (0.9)	5 (0.3)
Median Exposure (months)	15.34	17.49		15.34	17.49
Overall Exposure (patient-months)	**16,571**	**30,688**		**16,571**	**30,688**

1 Numbers not cumulative; patients counted only once in their final treatment category
2 Includes all patients exposed for at least the stated duration
Source: Applicant's Table 6, ISS

For Type 1 patients <18 years of age, the following total subject-months of exposure occurred:

- inhaled insulin, controlled Phase 2/3 trials: 690 patient-months for 153 patients
- SQ insulin, controlled Phase 2/3 trials: 663 patient-months for 148 patients
- inhaled insulin, all Phase 2/3 trials: 6,242 patient-months for 291 patients

7.2.1.2 Demographics

The distribution of common baseline demographic characteristics does not suggest problems with randomization. Among Type 1 diabetics, few non-Caucasians participated. A larger percentage of the Type 2 population was either black or Hispanic, although the vast majority of patients were Caucasian. In the U.S. diabetic population, Type 1 diabetics are much more likely to be Caucasian than non-Caucasian. Type 2 diabetes, however, is increasing in incidence in all racial groups, but especially among African Americans and Hispanics. The underlying cause of this increasing incidence is less tied to race *per se* than it is to a more rapidly increasing incidence of obesity in these groups, although certain racial groups (e.g. Pima Indians) have a stronger genetic predisposition. Because the etiology of the increasing incidence of Type 2 diabetes in most racial and ethnic groups in the United States is related to obesity rather than to

race, data obtained in this development program can likely be extrapolated to most obese Type 2 diabetics, despite the predominance of Caucasians in the clinical trials.

Table 7.2.1.2 Demographic Characteristics, Adult Patients, Controlled Phase 2/3 Studies

	Number (%) of Subjects				
	Type 1		Type 2		
	INH	SC	INH	SC	OA
N	698	705	1,277	488	644
Gender [number (%) of subjects]:					
Male	390 (55.9)	385 (54.6)	795 (62.3)	307 (62.9)	361 (56.1)
Female	308 (44.1)	320 (45.4)	482 (37.7)	181 (37.1)	283 (43.9)
Age (yr):					
Mean	38.0	38.0	57.2	55.6	56.6
Range	18-65	18-65	28-80	23-78	29-80
Race [number (%) of subjects]:					
White	616 (88.3)	642 (91.1)	1,043 (81.7)	348 (71.3)	569 (88.4)
Hispanic	43 (6.2)	35 (5.0)	94 (7.4)	63 (12.9)	28 (4.3)
Black	24 (3.4)	11 (1.6)	85 (6.7)	46 (9.4)	23 (3.6)
Asian	7 (1.0)	6 (0.9)	21 (1.6)	11 (2.3)	12 (1.9)
Other	8 (1.1)	11 (1.6)	34 (2.7)	20 (4.1)	12 (1.9)
BMI* (kg/m^2):					
Mean	25.3	25.3	30.2	30.1	30.4
Range	18-36	17-35	18-51	20-40	18-57

*Body Mass Index
INH=inhaled insulin, SC=subcutaneous short-acting insulin, OA=oral antidiabetic agents, and N= number of subjects.
Source: Appendix Tables 3.1.1.1.2 and 3.1.1.2

For the most part, exclusion criteria used in Phase 2 and Phase 3 trials were unlikely to limit the general applicability of trial results. However, the following exclusion criteria could have excluded significant numbers of diabetics who might be encountered in clinical practice:

- BMI >35 kg/m^2 for Type 2 diabetics
- HbA1c >12%
- Renal impairment
- Requirement of >150 units per day of subcutaneous insulin
- Signs of autonomic neuropathy, such as gastroparesis or orthostatic hypotension
- Tobacco smoking within 6 months of study or during study
- Two or more serious hypoglycemic episodes within the year prior to study
- Hospitalization or emergency room visit within the six months prior to study for poor diabetes control

Information regarding the safety of large doses of inhaled insulin, such as that required for very obese patients, and those who have already demonstrated a high subcutaneous requirement, is lacking. Significant renal impairment and autonomic neuropathy are common complications of diabetes. Although the applicant proposes in its label to exclude smokers from use of inhaled insulin, it is likely that smokers will use the drug, either because the smoking exclusion is not

noted by their physician, or because smokers may be unwilling to share their smoking history with their physician.

In controlled Phase 2/3 studies, mean duration of diabetes at diagnosis was similar for inhaled insulin and SQ patients for Type 1 patients (means 18.5 years for inhaled, 18.3 for SQ), but differed somewhat for Type 2 patients. Patients who were eligible for oral agent studies would be expected to have a shorter duration of diabetes than patients who had failed oral agents and required subcutaneous insulin. The overall Type 2 inhaled insulin population was a mix of patients who were and were not insulin-requiring at study entry; mean duration of diabetes for this group would be expected to be intermediate to the durations of diabetes for the SQ and OA groups. This was the case for Type 2 diabetics, with mean durations of diabetes of 10.6, 13.4 and 7.9 years respectively for inhaled, SQ and OA patients.

Overall, results of Phase 2 and Phase 3 trials are applicable to patients with uncomplicated diabetes, but it is unclear if these results may be extrapolated to patients with common diabetic complications, to the severely obese, or to very insulin-resistant patients.

7.2.1.3 Extent of exposure (dose/duration)

Extent of exposure by duration is presented above in Section 7.2.1.1.

For both Type 1 and Type 2 diabetics, the mean dose of long-acting insulin for inhaled insulin group patients was somewhat lower for inhaled insulin patients than for subcutaneous insulin patients. The mean dose of inhaled insulin gradually increased over time, while the dose of subcutaneous short-acting insulin increased from baseline to Month 3, and then remained stable until Month 12. It is difficult to attach particular significance to either of these observations. The mean lower dose of long-acting insulin for inhaled insulin patients implies that, on average, glycemic control was not disproportionately "carried" by the long-acting component of inhaled insulin patients' regimens. The gradual increase in inhaled insulin dose without a corresponding increase in short-acting SQ dose could indicate developing resistance to the action of inhaled insulin, or neutralization of insulin action by insulin antibodies; or it could merely represent increasing familiarity and comfort with upward titration of a novel agent. In major diabetes trials, such as UKPDS and DCCT, insulin dose tended to increase gradually over time; however, it is not clear why this occurred in the inhaled insulin group here and not in the SQ group.

Table 7.2.1.3.1 Summary of Average Total Daily Insulin Dose and Dose per Kg of Body Weight, Adult Patients with Type 1 Diabetes, Controlled Phase 2/3 Studies

	INH				SC Insulin			
	Dose LA (Dose/kg)		Dose SA (Dose/kg)		Dose-LA (Dose/kg)		Dose SA (Dose/kg)	
	N	Mean	N	Mean	N	Mean	N	Mean
Study 1022								
Baseline	288	30.68 (0.42)	287	22.59 (0.30)	285	32.94 (0.45)	286	23.91 (0.32)
Month 3	280	30.48 (0.41)	280	10.46 (0.14)*	285	34.98 (0.48)	285	25.09 (0.33)
Month 6	271	30.58 (0.41)	271	11.51 (0.15)*	278	35.40 (0.48)	279	25.08 (0.33)
Month 9	254	31.02 (0.41)	256	12.00 (0.16)*	266	35.39 (0.48)	267	24.92 (0.33)
Month 12	243	30.66 (0.41)	243	12.68 (0.17)*	258	35.69 (0.47)	262	25.37 (0.33)
					INH			
	Phase 2 Extension: 48-month completers				Study 111: 24-month completers			
Month 3			31	11.04 (0.15)*			244	11.14 (0.14)*
Month 6			31	11.86(0.16)*			244	11.95 (0.15)*
Month 12			31	12.94 (0.17)*			244	13.64 (0.18)*
Month 18			31	14.51 (0.20)*			244	14.76 (0.19)*
Month 24			31	14.55 (0.19)*			244	15.20 (0.19)*
Month 30			31	14.48 ((0.19)*				
Month 36			31	14.47 (0.19)*				
Month 42			31	15.35 (0.20)*				
Month 48			31	15.14 (0.20)*				

*Dose in mg (mg/kg where body weight was available for subject)
LA=long-acting; N=number of subjects with dosing information (not all subjects may have had body weight measured at each timepoint); SA=short-acting.
Source Data: Module 2.7.3, Appendix Tables 5.4.2.1, 5.5.2.1, 1022 CSR: Tables 5.10.1.2, 5.10.2.2, 111 CSR: Section 11, Item 11 Tables 1.3.1.4, 1.3.3.4.

Table 7.2.1.3.2 Summary of Average Total Daily Dose and Dose per Kg of Body Weight, Type 2 Diabetics, Controlled Phase 2/3 Studies

	INH				SC Insulin			
	Long-acting Dose (Dose/kg)		Short-acting Dose (Dose/kg)		Long-acting Dose (Dose/kg)		Short-acting Dose (Dose/kg)	
	N	Mean	N	Mean	N	Mean	N	Mean
Study 1029								
Baseline	307	43.1(0.5)	308	27.4 (0.3)	302	43.8 (0.5)	301	26.7 (0.3)
Month 3	301	44.3 (0.5)	301	12.7 (0.1)*	298	47.8 (0.5)	300	31.5 (0.4)
Month 6	289	43.9 (0.5)	289	13.2 (0.1)*	290	47.1 (0.5)	292	32.0 (0.4)
Month 9	272	43.6 (0.5)	273	13.5 (0.2)*	280	47.8 (0.5)	282	31.6 (0.4)
Month 12	235	44.8 (0.5)	235	14.7 (0.2)*	239	47.9 (0.5)	242	33.0 (0.4)
					INH			
Study 1001 and 1002 – 2 Year								
Week 10			444	11.7 (0.14)*				
Week 18			431	12.5 (0.14)*				
Week 24			439	12.8 (0.15)*				
Week 36			329	13.8 (0.16)*				
Week 52			314	14.7 (0.17)*				
Week 65			168	15.4 (0.18)*				
Week 78			167	15.6 (0.18)*				
Week 91			161	15.9 (0.18)*				
Week 104			154	16.8 (0.19)*				
	Phase 2 Extension: 48-month completers				Study 111: 24-month completers			
Month 3			58	13.81 (0.15)*			397	16.33 (0.18)*
Month 6			58	14.34 (0.16)*			397	17.05 (0.18)*
Month 12			58	15.81 (0.17)*			397	18.11 (0.19)*
Month 18			58	15.47 (0.17)*			397	18.78 (0.20)*
Month 24			58	16.47 (0.17)*			397	19.46 (0.21)*
Month 30			58	15.98 (0.17)*				
Month 36			58	16.98 (0.18)*				
Month 42			58	17.00 (0.18)*				
Month 48			58	17.15 (0.18)*				

*Dose in mg (mg/kg where body weight was available for subject)
N=number of subjects with dosing information (not all subjects may have had body weight measured at each timepoint).
Source Data: Module 2.7.3, Appendix Tables 4.2.8, 5.4.2.2, 5.5.2.2, 1029 CSR: Tables 5.10.1.2, 5.10.2.2, 111 CSR: Section 11, Item 11 Tables 1.3.1.6, 1.3.3.6; Study 1001/1002 (2-year): Table 1.5.10.1

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Reports of all published clinical trials of Exubera® were included in the NDA.

7.2.2.2 Postmarketing experience

Not applicable.

7.2.2.3 Literature

The clinical reviewer conducted an extensive literature search to look for safety information. No additional adverse events related to Exubera® were found in the medical literature as of 20 Jun 05. Other articles are referenced in the appropriate sections of the review.

7.2.3 Adequacy of Overall Clinical Experience

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The pharmacologic toxicology review is ongoing as of 6 Jul 05. The lack of an animal carcinogenicity study is of potential concern, because insulin is a growth factor, and the single-cell lining of the lung is receiving a large dose of a protein powder when inhaled insulin is administered. The higher frequency of adverse events of cough, and the brisk antibody response seen with this inhaled insulin product suggest that it has a chronic irritant effect. Certain other inhaled chronic irritants are carcinogenic to the lung. The mean duration of study for inhaled insulin patients may have been too short to assess the human carcinogenic potential of inhaled insulin. However, Dr. Alavi, the animal toxicology reviewer, states that it is unlikely that animal carcinogenicity studies would have resolved questions regarding human carcinogenic potential, due to problems administering the drug chronically via inhalation to rodents, and due to a potential nonrelevant tumorigenic response in rodents, which have insulin receptors in the lung.

7.2.5 Adequacy of Routine Clinical Testing

In general, routine clinical testing was adequate. The applicant has been asked to provide additional clinical data for marked laboratory outliers noted by the clinical reviewer.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The biopharmaceutics review is ongoing as of 7 Jul 05. The clinical reviewer has concerns regarding the lack of dose proportionality and dose equivalence seen with Exubera®, and feels that these could lead to an increased risk for hypoglycemia, and to problems with titration. Recommendations for a method of titration are needed for labeling; if the applicant is unable to construct a useful algorithm based on available PK/PD data, a study to determine the optimal titration method might be useful.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

In general, the data provided by the applicant appear adequate to allow characterization of adverse events associated with Exubera®. However, the extent of pulmonary safety data contained in the NDA falls far short of the amount that was repeatedly requested by the Division of Pulmonary and Allergy Drug Products. It remains to be seen whether the data submitted will be adequate for a pulmonary safety evaluation.

7.2.8 Assessment of Quality and Completeness of Data

An enormous volume of data was submitted by the applicant in this NDA. Some important summary and database information was missing, however. During review, the clinical reviewer noted errors in certain of the applicant's tables and figures that limited the interpretability of these data sources. In general, the applicant has been responsive in submitting missing and corrected data, but submissions related to several requests took weeks or months to arrive, and some have still not been received as of 12 Jul 05. Applications are expected to be complete at the time of initial NDA submission; piecemeal and delayed submission of new and corrected data has significantly complicated review of this application.

7.2.9 Additional Submissions, Including Safety Update

The applicant submitted a safety update on 27 Apr 05.

Two additional patients had died between the original safety data cut-off date of 1 Sep 04 and the safety update cut-off of 13 Dec 04; both patients were in subcutaneous insulin treatment groups.

The reported types of adverse events, and the frequency of these adverse events, appeared to be similar to those noted in the original NDA submission. However, the applicant provided only summary tables, and did not provide updated datasets to permit complete review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

A total of 22 deaths occurred among 3,603 subjects (0.6%) exposed to inhaled insulin in the clinical development program, as of the safety cut-off date of 1 Sep 04. Of these, 21 patients were participants in the clinical development program and one was a neonate born of a mother exposed to inhaled insulin. Ten deaths, including that of the neonate, occurred during controlled Phase 2/3 trials, which included 1,975 adult patients (0.5%). Twelve deaths occurred during extension studies, which included 1,449 patients (0.8%). Five patients who received comparator drugs died, out of 1,938 comparator patients (0.3%). When taking into account the longer duration of exposure for inhaled insulin groups, there is little difference in mortality rates between inhaled insulin and comparator treatments.

Of the adult patients who died during the clinical development program, 15/21 appear to have died of cardiac causes. Most diabetics die of cardiovascular disease, and the percentage of deaths which were due to cardiovascular disease during the study of this product is consistent with the usual incidence of cardiovascular death among diabetics. Those patients who died of acute causes do not appear to have had an unusually high incidence of severe hypoglycemic events (those requiring the assistance of another person, or events with a blood sugar <36 mg/dL). However, four of these patients had histories of a large number of nonserious hypoglycemic events prior to death, and one death occurred shortly after what appears to have been a hypoglycemic episode. Overall, the deaths which occurred in inhaled insulin group patients do not seem to have a stronger association with hypoglycemia than that expected in

diabetics treated with subcutaneous insulin. A total of 7/21 total deaths occurred in Type 1 diabetics who were taking inhaled insulin. The rate of death among Type 1 inhaled insulin patients does not exceed that found in the intensive treatment groups of large randomized trials in Type 1 diabetics. No clear difference was demonstrated between inhaled insulin and comparator patients for incidence or cause of death.

In controlled Phase 2 and Phase 3 studies in adult Type 1 patients, serious adverse events occurred at a slightly higher frequency in SQ group patients than in inhaled insulin group patients. The most common serious adverse events among Type 1 patients were hypoglycemia and loss of consciousness. In the controlled Phase 2/3 population, these occurred with slightly greater frequency in SQ patients than in inhaled insulin patients. In Type 1 adult patients, no pattern emerged of a single type of serious nonpulmonary adverse event, or grouping of serious nonpulmonary adverse events, that occurred with significantly greater frequency among inhaled insulin group patients than among SQ patients. Pulmonary serious adverse events will be discussed separately in Dr. Seymour's review. Event terms such as accidents and injuries that could potentially be related to hypoglycemia did not occur more frequently in Type 1 adult patients receiving inhaled insulin, and appear to have occurred less frequently numerically among inhaled insulin patients than among patients receiving SQ insulin.

In controlled Phase 2 and Phase 3 studies in Type 2 patients, serious adverse events occurred with approximately equal frequency among inhaled insulin patients and comparator patients. Myocardial infarction, chest pain, angina and hypoglycemia were the most common SAE terms among Type 2 patients. Inhaled insulin group patients did not have a significantly higher frequency of serious nonpulmonary adverse event term groupings of interest, such as terms related to coronary artery disease, hypoglycemia, loss of consciousness, seizure, accidents, injuries, neoplastic events, or immune system disorders. Hypoglycemia adverse event terms occurred numerically more frequently among SQ patients than among inhaled insulin patients or OA patients. Pulmonary adverse event term groupings will be addressed in Dr. Seymour's pulmonary review.

Hypoglycemia reported as a serious adverse event occurred somewhat more frequently among children taking inhaled insulin than among children taking SQ insulin. Otherwise, no single type of serious adverse event or grouping of adverse events occurred more frequently among pediatric patients taking inhaled insulin than among pediatric patients taking SQ only. Almost all serious adverse events among pediatric patients were related to hypoglycemia. Severe hypoglycemia was reported as a serious adverse event term more frequently among pediatric patients than among either adult Type 1 or Type 2 patients.

When evaluating serious hypoglycemic adverse events, the clinical reviewer also considered whether the nature of serious hypoglycemic adverse events differed between inhaled insulin and comparator patients. The clinical reviewer examined all adverse event narratives provided by the applicant, and identified those events which had serious accompanying events, e.g. loss of consciousness, syncope, accidents and injuries. Adult inhaled insulin group patients do not appear to have had a higher incidence of potentially dangerous accompanying events to serious hypoglycemic episodes than did comparator patients.

For further evaluation of serious adverse events, the clinical reviewer compared the event terms used by the applicant in its serious adverse event listings to the terms used by the investigators. This was done in order to ascertain whether the nature of serious adverse events could have been downplayed in the inhaled insulin groups, or embellished in the comparator groups. Upon review of all serious hypoglycemic event narratives, the clinical reviewer noted some cases in which the event was reported only as hypoglycemia, and an accompanying accident or injury was not mentioned in the listing. Although the serious adverse event listings for hypoglycemic events sometimes did not include mention of an accompanying accident or injury, this reconciliation difference did not occur more frequently among inhaled insulin patients than among comparator patients. Terms used for other types of serious adverse events in the applicant's serious adverse event listings almost always reconciled closely with those found in provided event narratives.

Because diabetic ketoacidosis is the leading cause of mortality among pediatric Type 1 diabetics, it was an event of significant interest. No deaths from diabetic ketoacidosis occurred in children in this development program, and no cases of cerebral edema accompanying DKA were reported. Pediatric serious adverse events of diabetic ketoacidosis did not occur more frequently among inhaled insulin patients than among SQ patients in controlled Phase 2/3 trials (one case among inhaled insulin patients, two cases among SQ patients). In the extension Study 111, a total of 21 serious adverse events of ketoacidosis occurred among 17 patients. This study had a large total duration of exposure for pediatric patients, with a total of 5,801 subject-months of exposure. Comparative incidence rates for DKA were 0.04 cases of diabetic ketoacidosis per child-year for inhaled insulin patients in all Phase 2/3 trials and 0.04 cases of DKA per child-year for SQ patients in controlled Phase 2/3 trials. In the medical literature, the reported incidence of DKA (after initial diagnosis) ranges from 1-10% per year (Dunger 2003).

When considering all adverse events (serious and nonserious), in controlled Phase 2/3 studies in Type 1 diabetics, the overall incidence of adverse events was similar between inhaled insulin patients and SQ patients, with 99.4% and 98.7% of patients, respectively, experiencing some type of adverse event. In controlled Phase 2/3 studies in Type 2 patients, adverse events occurred with nearly equal frequency between inhaled insulin patients [93.7% with event(s)] and SQ patients [96.7% with event(s)]. Among Type 2 patients treated with oral agents, 81.7% experienced an adverse event. This lower rate among oral-agent treated patients is due to a lower rate of hypoglycemia among these patients than among inhaled insulin or SQ patients.

Hypoglycemia was the most common adverse event among Type 1 patients, and occurred with equal frequency in inhaled insulin and SQ group patients. Cough was a common adverse event, and occurred with significantly greater frequency among inhaled insulin patients (196/698, 28.1%) than among SQ patients (59/705, 8.4%). Other respiratory adverse events (dyspnea, respiratory disorder) also occurred with greater frequency among inhaled insulin patients. Nasopharyngeal adverse events (epistaxis, pharyngitis, rhinitis, sinusitis) occurred at a higher frequency in inhaled insulin groups (310/698, 44.4%) than in SQ groups (220/705, 31.2%). Adverse event terms related to accidents occurred with equal frequency between groups. The event term "allergic reaction" occurred with slightly greater numeric frequency in inhaled insulin patients (31/698, 4.4%) than among SQ patients (23/705, 3.3%).

Among Type 2 patients, hypoglycemia was the most common adverse event term, and occurred most commonly in SQ patients (360/488, 73.8%). Inhaled insulin patients had a lower rate of hypoglycemic events than SQ patients, but had a higher rate than OA patients [inh ins = 794/1277 (62.2%), OA = 185/644 (28.7%)]. Cough was also very common, and occurred with significantly higher frequency among inhaled insulin patients than among comparator patients (inh ins 21.0%, SQ 7.4%, OA 3.7%). Accident and injury terms occurred numerically more frequently among SQ patients than among other groups. Several respiratory events (e.g. asthma, bronchitis, dyspnea) had a somewhat higher frequency among inhaled insulin patients than among comparator patients; please see Dr. Seymour's pulmonary review for discussion. Headache and paresthesia occurred at a slightly higher numeric rate in inhaled insulin groups than in comparator groups.

Hypoglycemic event rates did not differ between pediatric inhaled insulin and SQ patients. Among pediatric patients, the adverse event term seen with the greatest excess frequency for inhaled over SQ was cough. Nausea, headache and dizziness also occurred numerically more frequently in inhaled insulin patients than in SQ patients. When combining ear terms, adverse events related to the ear occurred more frequently in children in inhaled insulin groups than in SQ groups. The terms ear pain, ear disorder and otitis media had a combined event rate of 18/153 (11.8%) in the inhaled insulin patients vs 7/148 (4.7%) in SQ patients. This difference could be due to chance; however, the Eustachian tube in children provides an anatomically more direct route to the middle ear than does the Eustachian tube of the adult, and the possibility of entry of inhalation powder into the Eustachian tube of children is a consideration.

Common adverse events which seem likely to be related to inhaled insulin use include cough; nasopharyngeal adverse events such as pharyngitis, rhinitis and sinusitis; and certain respiratory adverse events such as dyspnea. Adverse events related to the ear seem to be related to inhaled insulin in children.

There is no clear relationship between age and incidence of rhinitis or sinusitis in patients exposed to inhaled insulin, and dose-dependency was not demonstrated. Inhaled insulin patients who developed rhinitis did so sooner than SQ patients who developed rhinitis.

Regarding serious but rare adverse events, the events "eye hemorrhage" and "retinal hemorrhage" occurred more frequently per unit of patient-time over all Phase 2/3 trials than these events occurred per unit of patient time in comparator groups in the controlled Phase 2/3 trials. Events termed "allergic reaction" occurred at a somewhat higher frequency per unit of patient-time among inhaled insulin patients in the population of all Phase 2/3 trials than among comparator patients in the controlled Phase 2/3 trials. Concern exists for the development of undesirable immune responses to inhaled insulin. Malignant neoplasms did not occur with greater frequency in inhaled insulin patients per unit of patient-time than in comparator patients.

Hypoglycemia reported as a serious adverse event was discussed above with other serious adverse events. Hypoglycemia was also evaluated by two specified definitions. Hypoglycemia was a secondary outcome measure in the major trials, with a study-specific definition. There

was also a definition of severe hypoglycemic events for the overall safety evaluation, in which severe hypoglycemia was defined as a hypoglycemic event in which the subject had a measured blood glucose of ≤ 36 mg/dL and/or required assistance.

For adult Type 1 patients overall, inhaled insulin was not associated with a higher rate of severe hypoglycemia was SQ insulin. However, in Study 107, the "intensive control" study in Type 1 diabetics, the applicant reported that severe hypoglycemic events did occur more frequently in the inhaled insulin group than in the SQ only group. This is a potentially important finding, because intensive control is now the standard of care for Type 1 diabetics, and severe hypoglycemia tends to be the limiting factor in achieving tight control. Severe hypoglycemia is associated with higher rates of accidents, injuries and other acute serious adverse events. If a new treatment for Type 1 diabetes is noninferior, but not superior, in efficacy to the standard of care of intensive subcutaneous insulin management, the new treatment's rate of severe hypoglycemia should not be significantly higher than that seen with the standard of care. That, however, did not appear to be the case in Study 107, where inhaled insulin was noninferior (but not superior) to subcutaneous insulin in efficacy, but was associated with a higher rate of severe hypoglycemic events by the applicant's analysis. It should be noted that the FDA Biostatistics reviewer calls into question the statistical model used by Pfizer for comparison of hypoglycemic event rates. Reanalysis by the FDA Biostatistics reviewer is ongoing, but it appears that a more appropriate model may show that severe hypoglycemia event rates did not actually differ between treatment groups.

Among Type 1 diabetics overall, in both the inhaled insulin and SQ groups, overall hypoglycemia (severe and nonsevere) event rates declined over time, with similar rates of decline between groups. This could indicate an initial period of adjustment to the study regimen, with declining incidence of severe hypoglycemic events as the study progressed, or a decline in reporting of clinical events. Although there was an apparent decline over time in controlled Phase 2/3 studies, severe hypoglycemic adverse events continued to occur in extension studies; the occurrence of severe hypoglycemic adverse events cannot be entirely attributed to an initial learning period for inhaled insulin.

Among Type 1 diabetics, inhaled insulin group patients tended to have higher hypoglycemic event rates in the early morning than did SQ group patients, while the converse was true for midday. This pattern was noted for the overall pattern in Phase 2 and Phase 3 trials, and held true across most studies. The reason for this consistent pattern of prebreakfast hypoglycemia in inhaled insulin group patients is unclear. One would expect prebreakfast hypoglycemia to be related to evening dosing of longacting insulin, rather than to the patient's shortacting insulin. However, in Study 107, the intensive control study in Type 1 diabetics, mean dose of longacting insulin was actually somewhat lower for inhaled insulin group patients, both for the evening dose and for the total daily dose. Study 1026 was the only study in which 0200 blood sugars were routinely measured. In this study, hypoglycemia was more common at 0200 for inhaled insulin group patients than for SQ patients. For the overall population of Type 1 diabetics in all Phase 2/3 studies, the majority of hypoglycemic episodes reported as serious adverse events among inhaled insulin patients occurred in the early morning hours (for those patients for whom serious adverse event narratives were provided). Inhaled insulin appears to be more likely than SQ

insulin to cause severe hypoglycemia in intensive management of Type 1 diabetes; for unknown reasons, these severe hypoglycemic events among intensively managed inhaled insulin patients appear to occur more often in the early morning hours.

Overall, severe hypoglycemic events were less common among patients with Type 2 diabetes compared to patients with Type 1 diabetes. Inhaled insulin group patients were not more likely to experience severe hypoglycemic events than were SQ group patients, in studies of Type 2 patients who were using insulin at baseline. However, inhaled insulin group patients were more likely to experience severe hypoglycemia than were patients in oral agent comparator groups in studies of patients who were not insulin-using at baseline. Control of glycemia was in general better with inhaled insulin than with oral agents, and thus a higher rate of hypoglycemia would be expected. In Studies 104, 109 and 110, all severe hypoglycemic events occurred in inhaled insulin group patients.

In studies of Type 2 diabetics where SQ was used as a comparator, rates of hypoglycemia declined over time for both SQ and inhaled insulin patients. In studies of Type 2 diabetics where oral agents were used as a comparator, event rates were too low to distinguish a time trend. The applicant provided data regarding time of day of hypoglycemic events for Type 2 patients, but the number of events was too low to discern a trend for any particular time of day.

In Studies 106 and 1009, children and adolescents who were treated with inhaled insulin were somewhat less likely to experience protocol-defined hypoglycemia (severe or nonsevere) than patients who were taking SQ insulin. In Study 107, there was no demonstrated difference between groups. Protocol-defined severe hypoglycemic events did not occur more frequently among pediatric inhaled insulin patients in Studies 106 and 1009. In Study 107, there were 16 events of severe hypoglycemia in the inhaled insulin group, and 10 events in the SQ group. Although the risk ratio was 1.62 for occurrence of severe hypoglycemia for inhaled insulin-treated adolescents vs SQ-treated adolescents, the limits of the confidence interval fell on either side of 1, and therefore the difference between groups was not statistically significant. Overall, protocol-defined hypoglycemia, and protocol-defined severe hypoglycemia, did not occur statistically significantly more frequently in pediatric patients treated with inhaled insulin compare to those treated with SQ alone.

Dose dependency of adverse events was explored. Among Type 1 diabetics treated with inhaled insulin, increased sputum production may be dose-related. When one examines the overall incidence of accidents and fractures, these events occurred at a higher numerical rate in patients on higher doses of inhaled insulin than in patients on lower doses of inhaled insulin. This is of concern, because of the variability in delivered dose of the device; there could be a relationship between unpredictability of delivered dose and risk for hypoglycemia-associated injury. The problems with dose proportionality and dose equivalence could also lead to increased risk for hypoglycemia.

Among Type 2 diabetics, the incidence of dyspnea among inhaled insulin patients appeared to be dose-related. Several respiratory events occurred with lower frequency in patients who were taking <10 mg/day of inhaled insulin than in those taking ≥ 10 mg/day, but with roughly equal

frequency between patients taking 10-20 mg/day and those taking >20 mg/day. These events included total respiratory events, bronchitis, respiratory tract infection, and rhinitis. The overall incidence of cardiovascular events appeared to be dose-related, although no one type of event predominated. Accidental injury and fracture also appear to be dose-related, which is again a worrisome finding, possibly indicative of problems related to variability of delivered dose if these events occurred in the setting of hypoglycemia. Retinal disorders appear to be dose-related. The overall incidence of malignant neoplasms does not appear to be dose-related, nor does the incidence of any single malignancy. While the possible dose-relatedness of these events is concerning, these findings must be interpreted with caution. As Type 2 diabetes progresses, beta cell failure occurs with progressive loss of endogenous insulin secretion and increasing requirement for drug therapy, and eventually for increasing insulin requirement. A higher insulin requirement may be a reflection of duration of disease, which is in turn associated with aging; either duration of disease or aging could be associated with an increased incidence of many adverse events.

Time dependency of adverse events was also explored. Among Type 1 patients, for respiratory events in general, and for some specific respiratory events (cough, respiratory tract infection, rhinitis, sputum increased, epistaxis), the time interval in which these adverse events were more likely to be reported (per patient) was during the first 6 months of inhaled insulin treatment. Decreased reporting of these events in subsequent treatment time intervals could either be due to a true decrease in the occurrence of the event, to dropout due to the event, or to nonreporting by patients who felt they had already brought the event to the attention of investigators, and therefore did not report it again. For Type 1 patients, accidental injury, motor vehicle accidents, and accidental fractures were more likely to be reported (per patient) during the time interval beyond 24 months. This could be due to a true increase in the incidence of the events, or to longer per-patient exposure during this time period. Among Type 1 patients, hyperglycemia and hypoglycemia were more likely to be reported as adverse events (per patient) in the time interval of 0-6 months of inhaled insulin treatment. This may be due to the learning process involved in instituting a novel treatment. As with respiratory adverse events, decreased reporting of these metabolic events in subsequent treatment time intervals could either be due to a true decrease in the occurrence of the event, to dropout due to the event, or to nonreporting by patients who felt they had already brought the event to the attention of investigators, and therefore did not report it again. For Type 1 patients, retinal disorders were more likely to be reported (per patient) during the time interval beyond 24 months. This could be due to a true increase in the incidence of the events, or to longer per-patient exposure during this time period.

Among Type 2 patients, for respiratory events in general, and for some specific respiratory events (cough, respiratory tract infection, epistaxis), the time interval in which these adverse events were more likely to be reported (per patient) was during the first 6 months of inhaled insulin treatment. Accidental injuries and fractures were more likely to be reported (per patient) during the time interval beyond 24 months. Hypoglycemia was more likely to be reported as an adverse event (per patient) in the time interval of 0-6 months of inhaled insulin treatment. This may be due to the learning process involved in instituting a novel treatment. No clear temporal pattern emerged among Type 2 patients for malignant neoplasms in general or for any particular

neoplasm. For Type 2 patients, retinal disorders were more likely to be reported (per patient) during the time interval beyond 24 months.

Demographic interactions for adverse events were also explored. A summary of the observations for demographic differences for adverse events includes:

- Numbers of non-Caucasian patients were too small to permit meaningful comparisons between treatment groups.
- For Type 1 patients, the event "sputum increased" had a higher incidence in older patients and in males in inhaled insulin patients, than was seen in SQ patients.
- For Type 1 patients in the SQ group, overall respiratory events occurred with decreasing frequency by age group, but in inhaled insulin patients, overall respiratory events occurred with approximately equal frequency between age groups. For patients age 18 and older, overall respiratory events occurred more frequently among inhaled insulin group patients than among SQ patients.
- For Type 1 diabetic children, otitis media occurred more frequently in inhaled insulin group children than in SQ group children. Otitis media occurred with low and approximately equal frequency in adult Type 1 patients in both treatment groups.
- For Type 1 patients, the events "allergic reaction" and "diarrhea" occurred with higher frequency among males than among females in the inhaled insulin group. This gender difference was not apparent in comparator groups.
- For Type 2 patients, the event "dry mouth" appeared to decrease in incidence with age in inhaled and oral agent groups, but not in the SQ group.
- For Type 2 patients, for all treatment groups, women were more likely to experience cough than men; for both genders, cough occurred much more frequently in inhaled insulin group patients than in comparator patients.
- For Type 2 patients, the incidence of bronchitis increased by age group for inhaled insulin patients, but not for comparator patients.
- For Type 2 patients, accidental injury, hypoglycemia, and respiratory tract infection occurred more frequently in men than in women in the inhaled insulin group. This gender difference was not observed in the comparator groups.
- For Type 2 patients, paresthesia occurred more frequently in women than in men in the inhaled insulin group. This gender difference was not observed in the comparator groups.

Among these observations, those most likely to have clinical significance include:

- Otitis media in children appears related to inhaled insulin treatment.
- The incidence of bronchitis appears to increase by age group for inhaled insulin patients, but not for comparator patients.
- For Type 2 patients, accidental injury and hypoglycemia appear to occur more frequently in men than in women taking inhaled insulin. This gender difference was not observed in the comparator groups.

Across the development program, greater increases occurred in insulin antibody levels for patients taking inhaled insulin than for patients taking either subcutaneous insulin alone or oral agents alone. This observation led to concerns about potential clinical consequences of this

antibody formation. The following points can be synthesized from extensive data regarding insulin antibodies associated with inhaled insulin use, and the potential clinical consequences of these antibodies:

- Seroconversion rates were higher among inhaled insulin patients than among comparator patients. In studies in which a quantitative insulin antibody assay was used, 75% of all inhaled insulin patients who had undetectable insulin antibodies at baseline had measurable insulin antibodies at end of study or last measurement, while only 10% of comparator patients seroconverted. Seroconversion rates for inhaled insulin patients were higher among Type 1 patients than among Type 2 patients, and were higher among children than among adults.
- For both Type 1 and Type 2 patients, inhaled insulin was associated with higher end-of-study insulin antibody levels, and with greater change from baseline, than was SQ insulin.
- Among Type 1 inhaled insulin patients, pediatric patients had higher end-of-study insulin antibody levels and greater changes from baseline than did patients ≥ age 18 years. Among Type 1 inhaled insulin patients, female patients had higher end-of-study insulin antibody levels and greater changes from baseline than did male patients.
- Among Type 2 patients, patient who had been using injected insulin prior to study enrollment had higher insulin antibody levels at end of study, and greater changes from baseline, than did patients who had not been using injected insulin prior to study. Among Type 2 patients using inhaled insulin, insulin antibody levels appeared to correlate with age.
- Insulin antibodies were predominantly IgG for both inhaled insulin patients and comparator patients. Binding profile was consistent with low affinity, high binding capacity antibodies.
- In general, adverse events of an allergic nature tended to occur with similar frequency between inhaled insulin and SQ group patients. For Type 1 patients, the event terms "allergic reaction" and "rhinitis" occurred somewhat more frequently among inhaled insulin patients than among SQ patients.
- There were no apparent associations between insulin antibody levels and incidence of hypoglycemic events. Patients who had severe hypoglycemic events (by specific hypoglycemia event definition) did not tend to have higher antibody levels than patients who did not have severe hypoglycemic events.
- When examining those patients who had the highest insulin antibody titres (>2,000 μU/mL), 33/37 were Type 1 diabetics, and 11 were children. Three of these patients experienced adverse events of a potentially allergic nature (allergic bronchiolitis, dermatitis of face and arms, bilateral eyelid swelling). Among the Type 1 patients with high antibody titres, 9 patients experienced a total of 67 severe hypoglycemic events. These 9 patients represent 27% of the total Type 1 study population; in the overall controlled Phase 2/3 population, 17% of inhaled insulin patients experienced a severe hypoglycemic event. However, when one considers duration of exposure, patients with high antibody titres did not experience severe hypoglycemia more frequently than did the population of Type 1 patients in all Phase 2/3 trials.
- The applicant made extensive attempts to develop a neutralizing antibody assay, but was unable to do so. Development of neutralizing insulin antibodies might be associated with increasing insulin requirements or worsening indices of glycemic control. However, there

was no association between insulin antibody levels and HbA1c, postprandial glucose, fasting glucose or insulin requirement.
- The actual drug substance used did not exhibit inherent immunogenicity in , in which 476 insulin-naïve Type 2 patients were randomized to receive either) for one year. Rates of insulin antibody development did not differ between groups.
- Discontinuation of inhaled insulin resulted in a decline in insulin antibody levels, although levels did not return to normal by 12 weeks of followup.

Overall, it appears that although inhaled insulin patients demonstrate a brisk increase in insulin antibody levels, studies to date do not demonstrate a clinical correlate of this finding.

Observations of note regarding reasons for discontinuation among Type 1 diabetics include:
- In controlled trials, discontinuations due to adverse events were more common among inhaled insulin patients than among SQ patients.
- A large number of inhaled insulin patients withdrew consent during uncontrolled portions of Phase 2 and Phase 3 trials

Observations of note regarding reasons for discontinuation among Type 2 diabetics include:
- Discontinuations due to adverse events occurred slightly numerically more frequently among inhaled insulin patients than among SQ patients, but occurred with equal frequency between inhaled insulin patients and patients in oral agents groups.
- As noted with Type 1 patients, a large number of patients were discontinued from study for "withdrawn consent" in the uncontrolled portions of Phase 2 and Phase 3 trials.

In controlled Phase 2 and Phase 3 studies in Type 1 diabetics, the most common category of events leading to discontinuation was respiratory, and all discontinuations due to respiratory adverse events occurred in inhaled insulin group patients. When considering all Phase 2 and Phase 3 trials, both controlled and uncontrolled, respiratory events were again the most common category of adverse events leading to discontinuation, with a total of 21 (2.3%) of inhaled insulin group patients discontinuing due to respiratory AEs. Cough was the most common AE leading to discontinuation, accounting for 10 discontinuations (1.1% of all Ph 2/3 Type 1 patients).

In controlled Phase 2 and Phase 3 studies in Type 2 diabetics, the most common category of events leading to discontinuation was respiratory, and 26/28 discontinuations due to respiratory adverse events occurred in inhaled insulin group patients. When considering all Phase 2 and Phase 3 trials, both controlled and uncontrolled, respiratory events were again the most common category of adverse events leading to discontinuation, with a total of 42 (3.9%) of inhaled insulin group patients discontinuing due to respiratory AEs. Cough was the most common AE leading to discontinuation, accounting for 26 discontinuations (1.6% of all Ph 2/3 Type 2 patients). Three events of oropharyngeal irritation (glossitis, gingivitis, pharyngitis) resulted in discontinuation in controlled Phase 2/3 trials in inhaled insulin patients, with one additional discontinuation due to pharyngitis in extension trials. No discontinuations due to oropharyngeal irritation occurred in SQ or oral agent control patients. In controlled Phase 2 and Phase 3 trials

in Type 2 diabetics, discontinuations due to neoplasia did not occur more frequently among inhaled insulin group patients than among control patients.

The large number of patients for whom consent was withdrawn was of concern to the clinical reviewer, because it raised the question of whether some of these patients actually dropped out for adverse events, tolerability issues, device use problems, or other noteworthy reasons. Upon request, the applicant submitted further information regarding the actual wording that the patient or investigator gave as the reason for those discontinuations that were listed as due to "withdrawn consent", "patient no longer willing to participate in study" or "other". This information was not available for all patients. Most of these stated reasons did not relate to adverse events, tolerability issues, or device problems, but some did. When considering the group of those studies for which revised data for reasons for discontinuation were available, the apparently more frequent misclassification of discontinuation reasons among inhaled insulin patients led to greater differences between groups in the rates of discontinuation for:

- adverse events (greater difference in frequency for both Type 1 and Type 2)
- insufficient clinical response (greater difference in frequency for Type 1)

If investigators were unclear on how reasons for discontinuation should have been classified, one would expect that they would have misclassified reasons with approximately equal frequency in inhaled insulin and control groups. However, discontinuations due to adverse events and insufficient clinical response appear to have been misclassified more frequently for inhaled insulin patients than for comparator patients in the controlled Phase 2/3 population. This disparity in rates of apparent misclassification of reasons for discontinuation is unexplained, but raises a question of investigator reporting bias.

Temporary discontinuations due to adverse events were more common among Type 1 inhaled insulin patients than among Type 1 patients in SQ groups. For adult Type 1 patients in controlled Phase 2 and Phase 3 trials, 4.7% of inhaled insulin patients had temporary discontinuations due to adverse events, compared to 1.3% of SQ patients. The most common category of adverse events leading to temporary discontinuation among Type 1 diabetic inhaled insulin patients was respiratory, with 16 such events among inhaled insulin patients vs 1 such event in the SQ groups.

Temporary discontinuations due to adverse events were more common among Type 2 inhaled insulin patients (5.6% of patients) compared to Type 2 SQ group patients (1.6% of patients), but occurred with comparable frequency in patients in oral agent groups (6.8%). Again, the most common category of event leading to temporary discontinuation was respiratory, with 24 Type 2 subjects (1.9%) temporarily discontinuing inhaled insulin for respiratory reasons, vs 1 respiratory temporary discontinuation among SQ patients, and zero among oral agent patients. Temporary discontinuations due to hypoglycemia were also more common among Type 2 inhaled insulin patients, with 14 patients (1.1%) temporarily discontinuing due to hypoglycemia, vs 3 (0.6%) and 3 (0.5%) of SQ and oral agent patients, respectively. Temporary discontinuations due to digestive events, particularly diarrhea, occurred more frequently among Type 2 oral agent group patients.

The incidences of new or worsening laboratory abnormalities did not appear to differ between inhaled insulin group patients and comparator patients.

An intensive QTc study was not performed. From routine electrocardiograms from those studies for which postbaseline ECGs were obtained, mean changes in QTc were not significantly different between inhaled insulin and comparator patients in controlled Phase 2 and Phase 3 studies. From routine electrocardiograms, outlier abnormalities of the QTc interval did not occur more frequently among inhaled insulin patients than among comparator patients in controlled Phase 2 and Phase 3 studies. Among Adult Type 1 and Type 2 diabetics, there was little difference between groups for mean ECG changes in heart rate, PR interval or QRS width.

Mean pulse and blood pressure did not change substantially from baseline to last observation for adults patients, and there were no significant differences between treatment groups.

Type 2 patients who were insulin-using at study entry did not gain more weight with inhaled insulin than with comparator; in Study 108, SQ patients actually gained statistically significantly more weight (1.28 kg, 95% CI 0.6-1.96). However, inhaled insulin patients who were not using insulin at study entry did have statistically significantly greater weight gain than comparator patients in several studies. The difference in weight gain was most evident in Study 1001, in which add-on inhaled insulin was compared to add-on metformin.

Study 1007 was a clinical pharmacokinetic and pharmacodynamic study conducted in 10 gestational and 3 pregestational diabetic women. It was an open-label, randomized, two-period, two-treatment, crossover study. Each subject received a single morning fasting dose of either 9 U regular SQ insulin or 1 puff of 3 mg inhaled insulin, then no study insulin for 14 days (with continued usual management of their diabetes), then a single dose of cross-over study medication. Insulin Tmax was earlier with inhaled insulin administration than with regular SQ insulin. Cmax was 83% higher with inhaled insulin than with regular SQ. AUC_{0-360} was similar for both treatments. Insulin Tmax in this study was similar to that seen in nonpregnant diabetics in other studies, where Tmax ranged from 38-78 minutes. Fasting insulin Cmax in these women was also similar to fasting insulin Cmax seen in nonpregnant diabetics. Bioavailability of inhaled insulin relative to SQ was 10% based on geometric mean; this relative bioavailability is similar to that seen in nonpregnant women. Time to maximum decline in glucose was somewhat shorter for pregnant inhaled insulin patients in this study (210 minutes) than for nonpregnant Type 2 diabetics receiving inhaled insulin in Study 1004, where the time to maximum decline in glucose was 248 minutes. The maximum decline in glucose concentration was less in these pregnant diabetics exposed to inhaled insulin than it was in nonpregnant Type 2 diabetics in study 1004, but significant differences in baseline glucose levels and patient age limit the interpretability of this observation.

Clinically apparent spontaneous abortions occur in insulin-requiring diabetic women at a rate roughly twice that of the normal population of pregnant women (29.5% vs 10-15%) (Miodovnik 1988). In the Exubera® development program, 4/10 women who became pregnant while taking inhaled insulin had a spontaneous abortion. In Studies 106 and 107, mean end-of-study insulin antibody levels for Type 1 nonpregnant diabetic women were 32.6% binding (SD 22.46) for the

semiquantitative Mayo assay, and 435.0 µU/mL (SD 1194.2) for the quantitative Esoterix® assay. None of the women in the development program who had adverse pregnancy outcomes had known insulin antibody levels higher than these means.

The information obtained about human reproductive risk of Exubera® is not substantial enough at this time to conclude that Exubera® can cause fetal harm, and thus Pregnancy Categories D or X are not warranted. However, some information is available in pregnant women which could assist clinicians in decision-making about whether or not to choose Exubera® for the treatment of pregnant women. The clinical reviewer recommends the addition to the label of a summary of the known information about the pregnancy outcomes of women exposed to Exubera®.

Pharmacokinetic studies of inhaled insulin in hepatic and renal impairment were not submitted by the applicant.

Some data were submitted to characterize the use of inhaled insulin in COPD patients. Study 1005 compared inhaled insulin PK between healthy patients and those with COPD. Following administration of 3 mg of inhaled insulin, Cmax was greater (by up to 50%) in COPD patients than in healthy subjects. Tmax occurred 25-50 minutes earlier in COPD patients compared to normal subjects. Overall insulin exposure (AUC_{0-360}) was greater in COPD patients than in healthy subjects (by approximately 15%). Bioavailability of inhaled insulin was 11% in healthy controls compared to 23-25% in COPD patients.

As of 1 Sep 04, four patients with COPD had died; one of these was taking inhaled insulin and died of metastatic colon cancer. No asthma patients had died as of 1 Sep 04.

Hypoglycemia event rates did not differ between underlying lung disease patients (with COPD or asthma), and those without these disorders, for either inhaled insulin or comparator patients. Patients with either asthma or COPD who were taking inhaled insulin appeared to experience asthenia more frequently than comparator patients (with or without underlying lung disease), and more frequently than inhaled insulin patients without underlying lung disease. Otherwise, the small number of each type of event within the underlying lung disease groups precludes meaningful conclusions regarding other types of events.

Declines in FEV1 and DLco occurred more frequently among inhaled insulin patients than among control patients in the controlled Phase 2/3 population, and are further discussed in Dr. Seymour's pulmonary review. The clinical reviewer examined nonpulmonary adverse events in those patients who had significant declines in PFTs, defined as declines from baseline to last observation of ≥ 15% in FEV1, TLC or FVC, and/or ≥ 20% decline in DLco. Hypoglycemia rates (by study definition of requirement for assistance, or value <36 mg/dL) were similar between patients who had significant PFT declines and those who did not, for both inhaled insulin and comparator patients. Hypoglycemia rates among patients who had declines in PFTs were similar between inhaled insulin and comparator patients. Reported adverse events of hypoglycemia occurred more commonly in inhaled insulin patients who had significant declines in PFTs than in comparator patients who had significant declines in PFTs [154/218 (70.6%) vs 86/154 (55.8%)], but at an equal rate to that seen in comparator patients who did not have

significant declines in PFTs (1069/1512, 70.7%). Total cardiovascular events occurred at a higher rate in inhaled insulin patients who had a significant decline in PFTs (45/218, 20.6%) than in comparator patients who had a significant decline in PFTs (26/154, 16.9%) and comparator patients who did not have a significant decline in PFTs (202/1512, 13.4%). No single cardiovascular event occurred at a significantly higher rate among inhaled insulin patients who had significant declines in PFTs.

Tobacco smoking within six months prior to randomization was an exclusion criterion for Phase 2/3 studies. In clinical pharmacology studies (005, 016, 1003, 1020), inhaled insulin pharmacokinetics and pharmacodynamics were significantly different in smokers. In nondiabetic and Type 2 diabetic smokers, Cmax, Tmax and AUC of inhaled insulin was 2-5 fold higher than that of nonsmokers. Smoking cessation led to a decline in insulin exposure within 3 days of abstinence, with further attenuation over time; by 7 days, insulin exposure was near that seen in nonsmokers. Resumption of smoking after abstinence resulted, within 2-3 days, in increased exposure similar to that seen prior to smoking cessation. The applicant is concerned about these findings, and considers the potential for rapid changes in systemic insulin exposure to be a prohibitive risk associated with cigarette smoking. The applicant recommends that patients should abstain from smoking for at least 6 months before inhaled insulin treatment, and should remain abstinent during inhaled insulin treatment. However, in order to reduce the likelihood that smokers will use inhaled insulin, specific education of patients and providers may be needed, with enhanced emphasis on the risk. Physicians may overlook the smoking statement in a long product label, and patients sometimes do not share their smoking history with their physicians.

Animal carcinogenicity and reproductive toxicity studies were not performed. The lack of carcinogenicity data is a potential concern; insulin is a growth factor, and inhaled insulin appears to be a clinical lung irritant. Although no difference was noted between inhaled insulin and comparator groups for the incidence of lung carcinoma, the duration of study was shorter than the usual duration of time needed from an initial lung insult to the development of a malignancy. However, Dr. Alavi, the animal toxicology reviewer, states that it is unlikely that animal carcinogenicity studies would have resolved questions regarding human carcinogenic potential, due to problems administering the drug chronically via inhalation to rodents, and due to a potential nonrelevant tumorigenic response in rodents, which have insulin receptors in the lung.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The applicant pooled safety data from Phase 2 and Phase 3 studies for safety analyses, with separate analyses for Type 1 and Type 2 patients. Exclusion criteria were similar across studies.

Relative rates of severe hypoglycemia were similar across studies. Pooling of safety data, with separation into Type 1 and Type 2 diabetic groups, appears to have been appropriate.

7.4.1.2 Combining data

Because inhaled insulin exposure was much greater than that for comparators for the "All Phase 2/3" population, the clinical reviewer compared rates of events using patient-month exposure data when possible.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Among inhaled insulin patients in all Phase 2/3 studies, most adverse events in general did not appear to be dose-dependent. Among Type 1 diabetics, increased sputum production may be dose-related. When one examines the overall incidence of accidents and fractures, these events occurred at a higher numerical rate in patients on higher doses. This is of concern, because of the variability in delivered dose of the device, and the question of whether this could increase the risk for hypoglycemia-associated injury. However, the applicant did specifically examine all cases of serious accidents and injuries for possible relationship to hypoglycemia, and no difference between treatment groups was noted.

Table 7.4.2.1.1 Adverse Events by Daily Inhaled Insulin Dose at Time of Onset of Adverse Event, Adult Type 1 Patients, All Phase 2/3 Studies

	Inh Ins Dose (mg)		
	<10 # (%) of Patients with Event	**10-15 # (%) of Patients with Event**	**>15 # (%) of Patients with Event**
Respiratory (all events)	389 (58.7)	353 (53.8)	242 (55.3)
Cough	135 (20.4)	107 (16.3)	84 (19.2)
Respiratory disorder	39 (5.9)	35 (5.3)	29 (6.6)
Dyspnea	22 (3.3)	11 (1.7)	12 (2.7)
Asthma	7 (1.1)	7 (1.1)	7 (1.6)
Bronchitis	19 (2.9)	30 (4.6)	6 (1.4)
Pneumonia	5 (0.8)	5 (0.8)	6 (1.4)
Respiratory tract infection	209 (31.5)	215 (32.8)	151 (34.5)
Rhinitis	72 (10.9)	58 (8.8)	57 (13.0)
Sinusitis	47 (7.1)	30 (4.6)	39 (8.9)
Sputum increased	7 (1.1)	18 (2.7)	12 (2.7)
Chest pain	24 (3.6)	11 (1.7)	9 (2.1)
Dry mouth	9 (1.4)	8 (1.2)	6 (1.4)
Epistaxis	6 (0.9)	4 (0.6)	2 (0.5)
Accidental injury	61 (9.2)	63 (9.6)	46 (10.5)
Motor vehicle accident	1 (0.2)	2 (0.3)	0
Bone fracture accidental	18 (2.7)	17 (2.6)	21 (4.8)
Pathological fracture	0	0	1 (0.2)
Leukopenia	2 (0.3)	1 (0.2)	3 (0.7)
Convulsion	2 (0.3)	4 (0.6)	6 (1.4)
Grand mal convulsion	1 (0.2)	0	1 (0.2)
Coma	1 (0.2)	1 (0.2)	0

Table 7.4.2.1.1 Adverse Events by Daily Inhaled Insulin Dose at Time of Onset of Adverse Event, Adult Type 1 Patients, All Phase 2/3 Studies

	Inh Ins Dose (mg)		
	<10 # (%) of Patients with Event	**10-15 # (%) of Patients with Event**	**>15 # (%) of Patients with Event**
Diabetic coma	0	1 (0.2)	0
Hypoglycemia (reported as AE)	617 (93.1)	604 (92.1)	395 (90.2)
Hyperglycemia	7 (1.1)	5 (0.8)	4 (0.9)
Breast carcinoma	2 (0.3)	0	0
Source: Applicant's Table 4.2.4.1.1, Section 2.7.4			

Among Type 2 diabetics, the incidence of dyspnea appeared to be dose-related. Several respiratory events occurred with lower frequency in patients who were taking <10 mg/day of inhaled insulin than in those taking ≥ 10 mg/day, but with roughly equal frequency between patients taking 10-20 mg/day and those taking >20 mg/day. These events included total respiratory events, bronchitis, respiratory tract infection, and rhinitis. The overall incidence of cardiovascular events appeared to be dose-related, although no one type of event predominated. Accidental injury and fracture also appear to be dose-related, which is again a worrisome finding, possibly indicative of problems related to variability of delivered dose if these events occurred in the setting of hypoglycemia. Retinal disorders appear to be dose-related. The overall incidence of malignant neoplasms does not appear to be dose-related, nor does the incidence of any single malignancy.

While the possible dose-relatedness of these events is concerning, these findings must be interpreted with caution. As Type 2 diabetes progresses, beta cell failure occurs with progressive loss of endogenous insulin secretion and increasing requirement for drug therapy, and eventually for increasing insulin requirement. A higher insulin requirement may be a reflection of duration of disease, which is in turn associated with aging; either duration of disease or aging could be associated with an increased incidence of many adverse events.

Table 7.4.2.1.2 Adverse Events by Daily Inhaled Insulin Dose at Time of Onset of Adverse Event, Type 2 Patients, All Phase 2/3 Studies

	Inh Ins Dose (mg)		
	<10 # (%) of Patients with Event	**10-20 # (%) of Patients with Event**	**>20 # (%) of Patients with Event**
Respiratory (all events)	400 (38.4)	676 (53.6)	333 (51.7)
Cough	132 (12.7)	213 (16.9)	96 (14.9)
Respiratory disorder	43 (4.1)	72 (5.7)	46 (7.1)
Dyspnea	23 (2.2)	45 (3.6)	36 (5.6)
Asthma	14 (1.3)	33 (2.6)	13 (2.0)
Bronchitis	30 (2.9)	58 (4.6)	32 (5.0)
Lung fibrosis	0	0	1 (0.2)
Pneumonia	8 (1.6)	20 (1.6)	10 (1.6)
Respiratory tract infection	214 (20.5)	375 (29.8)	203 (31.5)
Rhinitis	50 (4.8)	107 (8.5)	50 (7.8)

Table 7.4.2.1.2 Adverse Events by Daily Inhaled Insulin Dose at Time of Onset of Adverse Event, Type 2 Patients, All Phase 2/3 Studies

	Inh Ins Dose (mg)		
	<10 # (%) of Patients with Event	**10-20 # (%) of Patients with Event**	**>20 # (%) of Patients with Event**
Sinusitis	43 (4.1)	82 (6.5)	44 (6.8)
Sputum increased	16 (1.5)	29 (2.3)	14 (2.2)
Cardiovascular (all events)	143 (13.7)	221 (17.6)	129 (20.0)
Chest pain	36 (3.5)	55 (4.4)	31 (4.8)
Dry mouth	15 (1.4)	19 (1.5)	3 (0.5)
Accidental fall	3 (0.3)	3 (0.2)	1 (0.2)
Accidental injury	67 (6.4)	110 (8.7)	76 (11.8)
Motor vehicle accident	0	2 (0.2)	0
Bone fracture accidental	11 (1.1)	25 (2.0)	18 (2.8)
Pathological fracture	0	1 (0.1)	1 (0.2)
Leukopenia	0	1 (0.1)	0
Convulsion	1 (0.1)	1 (0.1)	9 (1.4)
Hypoglycemia (reported as AE)	474 (45.4)	694 (55.1)	318 (49.4)
Hyperglycemia (reported as AE)	5 (0.5)	6 (0.5)	2 (0.3)
Weight gain (reported as AE)	10 (1.0)	19 (1.5)	17 (2.6)
Bladder carcinoma	0	1 (0.1)	0
Breast carcinoma	1 (0.1)	0	1 (0.2)
Endometrial carcinoma	0	1 (0.2)	0
Gastrointestinal carcinoma	1 (0.1)	1 (0.1)	0
Lung carcinoma	0	3 (0.2)	0
Lymphoma malignant	0	0	2 (0.3)
Melanoma	0	1 (0.1)	1 (0.2)
Prostate carcinoma	1 (0.2)	4 (0.5)	1 (0.2)
Renal carcinoma	0	1 (0.1)	0
Thyroid carcinoma	1 (0.1)	0	0
Eye hemorrhage	5 (0.5)	11 (0.9)	6 (0.9)
Retinal hemorrhage	2 (0.2)	6 (0.5)	3 (0.5)
Retinal detachment	1 (0.1)	0	0
Retinal disorder	23 (2.2)	49 (3.9)	28 (4.3)

Source: Applicant's Table 4.2.4.1.2, Section 2.7.4

7.4.2.2 Explorations for time dependency for adverse findings

Among Type 1 patients, for respiratory events in general, and for some specific respiratory events (cough, respiratory tract infection, rhinitis, sputum increased, epistaxis), the time interval in which these adverse events were more likely to be reported (per patient) was during the first 6 months of inhaled insulin treatment. Decreased reporting of these events in subsequent treatment time intervals could either be due to a true decrease in the occurrence of the event, to dropout due to the event, or to nonreporting by patients who felt they had already brought the event to the attention of investigators, and therefore did not report it again.

For Type 1 patients, accidental injury, motor vehicle accidents, and accidental fractures were more likely to be reported (per patient) during the time interval beyond 24 months. This could be due to a true increase in the incidence of the events, or to longer per-patient exposure during this time period.

Among Type 1 patients, hyperglycemia and hypoglycemia were more likely to be reported as adverse events (per patient) in the time interval of 0-6 months of inhaled insulin treatment. This may be due to the learning process involved in instituting a novel treatment. As with respiratory adverse events, decreased reporting of these metabolic events in subsequent treatment time intervals could either be due to a true decrease in the occurrence of the event, to dropout due to the event, or to nonreporting by patients who felt they had already brought the event to the attention of investigators, and therefore did not report it again.

For Type 1 patients, retinal disorders were more likely to be reported (per patient) during the time interval beyond 24 months. This could be due to a true increase in the incidence of the events, or to longer per-patient exposure during this time period.

Table 7.4.2.2.1 Prevalence of Adverse Events by Time Interval of Treatment, Adult Type 1 Patients, All Phase 2/3 Studies

	Interval of Treatment (months)				
	>0-6 # (%) of Patients with Event	**>6-12 # (%) of Patients with Event**	**>12-18 # (%) of Patients with Event**	**>18-24 # (%) of Patients with Event**	**>24 # (%) of Patients with Event**
Respiratory (all events)	604 (65.8)	312 (45.5)	266 (45.4)	172 (43.8)	129 (52.0)
Cough increased	215 (23.4)	56 (8.2)	46 (7.8)	41 (10.4)	34 (13.7)
Respiratory disorder	44 (4.8)	29 (4.2)	25 (4.3)	19 (4.8)	16 (6.5)
Lung disorder	0	0	1 (0.2)	1 (0.3)	1 (0.4)
Dyspnea	20 (2.2)	9 (1.3)	14 (2.4)	4 (1.0)	4 (1.6)
Asthma	6 (0.7)	7 (1.0)	9 (1.5)	5 (1.3)	4 (1.6)
Bronchitis	20 (2.2)	18 (2.6)	12 (2.0)	4 (1.0)	7 (2.8)
Pneumonia	3 (0.3)	4 (0.6)	6 (1.0)	2 (0.5)	1 (0.4)
Respiratory tract infection	324 (35.3)	163 (23.8)	154 (26.3)	82 (20.9)	76 (30.6)
Rhinitis	110 (12.0)	52 (7.6)	30 (5.1)	15 (3.8)	24 (9.7)
Sinusitis	53 (5.8)	23 (3.4)	29 (4.9)	15 (3.8)	15 (6.0)
Sputum increased	25 (2.7)	6 (0.9)	6 (1.0)	0	3 (1.2)
Epistaxis	9 (1.0)	4 (0.6)	1 (0.2)	0	2 (0.8)
Accidental injury	77 (8.4)	44 (6.4)	29 (4.9)	20 (5.1)	36 (14.5)
Motor vehicle accident	1 (0.1)	0	0	0	2 (0.8)
Bone fracture accidental	18 (2.0)	18 (2.6)	14 (2.4)	7 (1.8)	8 (3.2)
Pathological fracture	0	0	1 (0.2)	0	0
Leukopenia	0	1 (0.1)	2 (0.3)	2 (0.5)	2 (0.8)
Convulsion	1 (0.1)	6 (0.9)	2 (0.3)	2 (0.5)	1 (0.4)
Grand mal convulsion	2 (0.2)	0	0	0	0
Coma	1 (0.1)	1 (0.1)	0	0	0
Diabetic coma	1 (0.1)	0	0	0	0
Hypoglycemia (reported as AE)	889 (96.8)	618 (90.2)	521 (88.9)	345 (87.8)	220 (88.7)
Hyperglycemia (reported as AE)	12 (1.3)	2 (0.3)	0	1 (0.3)	1 (0.4)
Eye hemorrhage	5 (0.5)	1 (0.1)	4 (0.7)	1 (0.3)	2 (0.8)
Retinal detachment	0	0	0	1 (0.3)	0
Retinal disorder	9 (1.0)	5 (0.7)	6 (1.0)	5 (1.3)	6 (2.4)
Retinal hemorrhage	0	3 (0.4)	2 (0.3)	1 (0.3)	0

Table 7.4.2.2.1 Prevalence of Adverse Events by Time Interval of Treatment, Adult Type 1 Patients, All Phase 2/3 Studies

	Interval of Treatment (months)				
	>0-6 # (%) of Patients with Event	>6-12 # (%) of Patients with Event	>12-18 # (%) of Patients with Event	>18-24 # (%) of Patients with Event	>24 # (%) of Patients with Event
Breast carcinoma	1 (0.1)	1 (0.1)	0	0	0

Source: Applicant's Table 4.2.3.1.1, Section 2.7.4

Among Type 2 patients, for respiratory events in general, and for some specific respiratory events (cough, respiratory tract infection, epistaxis), the time interval in which these adverse events were more likely to be reported (per patient) was during the first 6 months of inhaled insulin treatment. Decreased reporting of these events in subsequent treatment time intervals could either be due to a true decrease in the occurrence of the event, to dropout due to the event, or to nonreporting by patients who felt they had already brought the event to the attention of investigators, and therefore did not report it again.

For Type 2 patients, accidental injuries and fractures were more likely to be reported (per patient) during the time interval beyond 24 months. This could be due to a true increase in the incidence of the events, or to longer per-patient exposure during this time period.

Among Type 2 patients, hypoglycemia was more likely to be reported as an adverse event (per patient) in the time interval of 0-6 months of inhaled insulin treatment. This may be due to the learning process involved in instituting a novel treatment. As with respiratory adverse events, decreased reporting of these metabolic events in subsequent treatment time intervals could either be due to a true decrease in the occurrence of the event, to dropout due to the event, or to nonreporting by patients who felt they had already brought the event to the attention of investigators, and therefore did not report it again.

No clear temporal pattern emerged among Type 2 patients for malignant neoplasms in general or for any particular neoplasm.

For Type 2 patients, retinal disorders were more likely to be reported (per patient) during the time interval beyond 24 months. This could be due to a true increase in the incidence of the events, or to longer per-patient exposure during this time period.

Table 7.4.2.2.2 Prevalence of Adverse Events by Time Interval of Treatment, Type 2 Patients, All Phase 2/3 Studies

	Interval of Treatment (months)				
	>0-6 # (%) of Patients with Event	**>6-12 # (%) of Patients with Event**	**>12-18 # (%) of Patients with Event**	**>18-24 # (%) of Patients with Event**	**>24 # (%) of Patients with Event**
Respiratory (all events)	807 (51.1)	534 (41.2)	384 (38.5)	289 (38.2)	212 (41.8)
Cough increased	265 (16.8)	117 (9.0)	77 (7.7)	59 (7.8)	43 (8.5)
Respiratory disorder	71 (4.5)	44 (3.4)	32 (3.2)	33 (4.4)	42 (8.3)
Lung disorder	1 (0.1)	1 (0.1)	2 (0.2)	1 (0.1)	2 (0.4)
Dyspnea	36 (2.3)	26 (2.0)	24 (2.4)	22 (2.9)	20 (3.9)
Asthma	24 (1.5)	16 (1.2)	15 (1.5)	13 (1.7)	11 (2.2)
Bronchitis	47 (3.0)	32 (2.5)	21 (2.1)	23 (3.0)	20 (3.9)
Lung fibrosis	0	0	1 (0.1)	0	1 (0.2)
Pneumonia	8 (0.5)	12 (0.9)	7 (0.7)	7 (0.9)	10 (2.0)
Respiratory tract infection	393 (24.9)	251 (19.4)	179 (17.9)	129 (17.0)	111 (21.9)
Rhinitis	104 (6.6)	50 (3.9)	42 (4.2)	33 (4.4)	39 (7.7)
Sinusitis	70 (4.4)	57 (4.4)	40 (4.0)	31 (4.1)	30 (5.9)
Sputum increased	30 (1.9)	21 (1.6)	13 (1.3)	3 (0.4)	8 (1.6)
Epistaxis	14 (0.9)	12 (0.9)	7 (0.7)	2 (0.3)	3 (0.6)
Cardiovascular (all events)	218 (13.8)	148 (11.4)	140 (14.0)	122 (16.1)	114 (22.5)
Angina	9 (0.6)	6 (0.5)	7 (0.7)	4 (0.5)	3 (0.6)
Chest pain	49 (3.1)	35 (2.7)	18 (1.8)	20 (2.6)	19 (3.7)
Myocardial infarction	9 (0.6)	2 (0.2)	7 (0.7)	2 (0.3)	8 (1.6)
Accidental fall	6 (0.4)	0	1 (0.1)	0	0
Accidental injury	114 (7.2)	56 (4.3)	53 (5.3)	43 (5.7)	47 (9.3)
Motor vehicle accident	1 (0.1)	0	0	1 (0.1)	0
Bone fracture accidental	21 (1.3)	18 (1.4)	14 (1.4)	9 (1.2)	13 (2.6)
Pathological fracture	1 (0.1)	1 (0.1)	0	1 (0.1)	1 (0.2)
Leukopenia	0	0	0	0	1 (0.2)
Convulsion	1 (0.1)	1 (0.1)	1 (0.1)	0	1 (0.2)
Hypoglycemia (reported as AE)	925 (58.6)	595 (45.9)	413 (41.4)	290 (38.3)	216 (42.6)
Hyperglycemia (reported as AE)	5 (0.3)	2 (0.2)	1 (0.1)	4 (0.5)	2 (0.4)
Weight gain (reported as AE)	27 (1.7)	19 (1.5)	17 (1.7)	14 (1.8)	9 (1.8)
Obesity	0	1 (0.1)	0	0	0
Bladder carcinoma	0	0	1 (0.1)	0	0
Breast carcinoma	0	2 (0.2)	0	0	0
Carcinoma	1 (0.1)	2 (0.7)	0	0	0
Endometrial carcinoma	0	0	0	1 (0.4)	0
Gastrointestinal carcinoma	0	0	1 (0.1)	2 (0.3)	0
Lung carcinoma	0	1 (0.1)	0	2 (0.3)	0
Lymphoma	0	0	0	1 (0.1)	2 (0.4)
Melanoma	0	1 (0.1)	1 (0.1)	0	0
Prostate carcinoma	1 (0.1)	1 (0.1)	1 (0.2)	2 (0.4)	2 (0.6)
Renal carcinoma	0	1 (0.1)	0	0	0
Thyroid carcinoma	1 (0.1)	0	0	0	0
Eye hemorrhage	7 (0.4)	9 (0.7)	3 (0.3)	3 (0.4)	4 (0.8)
Retinal detachment	0	1 (0.1)	0	0	0
Retinal disorder	28 (1.8)	32 (2.5)	30 (3.0)	35 (4.6)	36 (7.1)
Retinal hemorrhage	3 (0.2)	2 (0.2)	3 (0.3)	1 (0.1)	4 (0.8)

Table 7.4.2.2.2 Prevalence of Adverse Events by Time Interval of Treatment, Type 2 Patients, All Phase 2/3 Studies

	Interval of Treatment (months)				
	>0-6 # (%) of Patients with Event	**>6-12 # (%) of Patients with Event**	**>12-18 # (%) of Patients with Event**	**>18-24 # (%) of Patients with Event**	**>24 # (%) of Patients with Event**
Retinal vascular disorder	0	0	0	1 (0.1)	0

Source: Applicant's Table 4.2.3.1.2, Section 2.7.4

7.4.2.3 Explorations for drug-demographic interactions

The applicant provided demographic analyses of adverse events by age, race and gender. Events analyzed included those events that occurred at a higher frequency in inhaled insulin group patients than in SQ patients, in the controlled Phase 2/3 population. For Type 1 diabetics, the applicant analyzed cough, respiratory disorder, chest pain, dry mouth, dyspnea, epistaxis, hyperglycemia, and sputum increased. For Type 2 diabetics, events analyzed included cough, dry mouth, dyspnea, and sputum increased.

For Type 1 diabetics, the only event in the applicant's analysis that showed apparent differences in demographic patterns between inhaled insulin and SQ patients was "sputum increased", which showed a relative increased incidence among older patients and males in the inhaled insulin groups. There were too few non-Caucasians for meaningful comparisons between racial groups.

Table 7.4.2.3.1 Incidence of "Sputum Increased" by Age and Gender, Type 1 Diabetics, Controlled Phase 2/3 Studies

		Inh Ins n (%)	**SQ n (%)**
Age (years)	**< 18**	2 (1.3)	2 (1.4)
	18-44	19 (3.8)	6 (1.2)
	45-64	8 (4.2)	2 (1.0)
Gender	**Male**	20 (5.1)	3 (0.8)
	Female	7 (2.3)	5 (1.6)

Source: Applicant's Tables 13 and 14, ISS

For Type 2 diabetics, dry mouth appeared to decrease in incidence by age for both inhaled insulin and OA group patients. For all treatment groups, women were more likely to experience cough than men. Numbers of non-Caucasians were too small to permit meaningful comparisons.

Table 7.4.2.3.2 Incidence of "Sputum Increased" and Cough by Age and Gender, Type 2 Diabetics, Controlled Phase 2 and Phase 3 Studies

		Sputum Increased			Cough		
		Inh Ins	**SQ**	**OA**	**Inh Ins**	**SQ**	**OA**
Age (yrs)	**18-44**	3 (2.3)	1 (1.3)	1 (1.4)	34 (26.2)	3 (4.0)	2 (2.8)
	45-64	24 (2.8)	2 (0.7)	1 (0.2)	172 (20.2)	21 (6.9)	18 (4.2)
	65-74	6 (2.3)	1 (1.0)	1 (0.8)	59 (22.3)	11 (10.8)	4 (3.3)
	≥75	1 (3.3)	0	0	3 (10.0)	1 (12.5)	0
Gender	**Male**	23 (2.9)	4 (1.3)	1 (0.3)	140 (17.6)	21 (6.8)	12 (3.3)
	Female	11 (2.3)	0	2 (0.7)	128 (26.6)	15 (8.3)	12 (4.2)
Source: Applicant's Tables 24 and 25, ISS							

The clinical reviewer examined all adverse events by age and gender, and noted the following events that appeared to have an association with either age or gender for inhaled insulin patients. Rates in comparator patients are also provided.

Table 7.4.2.3.3 Additional Events with Possible Relationship to Age for Type 1 Diabetic Inhaled Insulin Patients, Controlled Phase 2/3 Trials

	Inh Ins			SQ		
Adverse Event	**<18 Yrs (total n = 153) n (%)**	**18-44 Yrs (total n = 506) n (%)**	**45-64 Yrs (total n = 190) n (%)**	**<18 Yrs (total n = 148) n (%)**	**18-44 Yrs (total n = 508) n (%)**	**45-64 Yrs (total n = 196) n (%)**
Accidental injury	23 (15.0)	55 (10.0)	22 (11.6)	27 (18.2)	58 (11.4)	21 (10.7)
Tremor	51 (33.3)	97 (19.2)	25 (13.2)	49 (33.1)	97 (19.1)	30 (15.3)
Overall Respiratory Events	112 (73.2)	377 (74.5)	137 (72.1)	104 (70.3)	319 (62.8)	108 (55.1)
Pharyngitis	34 (22.2)	97 (19.2)	25 (13.2)	31 (20.9)	83 (16.3)	19 (9.7)
Otitis media	10 (6.5)	2 (0.4)	2 (1.1)	5 (3.4)	7 (1.4)	1 (0.5)
Source: Applicant's Table 4.1.3.1.1, Section 2.7.4						

Accidental injury, tremor and pharyngitis occurred with decreasing frequency by age among Type 1 diabetics; this pattern did not differ between inhaled insulin and SQ groups. In the SQ group, overall respiratory events occurred with decreasing frequency by age, but in inhaled insulin groups, overall respiratory events occurred with approximately equal frequency between age groups. This suggests that, in Type 1 adults, respiratory adverse events are drug-related in inhaled insulin patients. Otitis media occurred more frequently in inhaled insulin group children than in SQ group children; in other age groups, otitis media occurred with low and roughly equal frequency between inhaled and SQ groups.

Table 7.4.2.3.4 Additional Events with Possible Relationship to Age for Type 2 Diabetic Inhaled Insulin Patients, Controlled Phase 2/3 Trials

	Inh Ins				SQ				OA			
Event	**18-44 Yrs N=130 n (%)**	**45-64 Yrs N=853 n (%)**	**65-74 Yrs N=264 n (%)**	**≥ 75 Yrs N=30 n (%)**	**18-44 Yrs N=75 n (%)**	**45-64 Yrs N=303 n (%)**	**65-74 Yrs N=102 n (%)**	**≥75 Yrs N=8 n (%)**	**18-44 Yrs N=72 n (%)**	**45-64 Yrs N=426 n (%)**	**65-74 Yrs N=122 n (%)**	**≥ 75 Yrs N=24 n (%)**
Accidental injury	13 (10.0)	66 (7.7)	18 (6.8)	1 (3.3)	8 (10.7)	31 (10.2)	14 (13.7)	2 (25.0)	3 (4.2)	30 (7.0)	6 (4.9)	2 (8.3)
Nausea	12 (9.2)	57 (6.7)	10 (3.8)	0	1 (1.3)	17 (5.6)	6 (5.9)	1 (12.5)	5 (6.9)	22 (5.2)	2 (1.6)	4 (16.7)
Hypoglycemia	76 (58.5)	533 (62.5)	165 (62.5)	20 (66.7)	56 (74.7)	223 (73.6)	75 (73.5)	6 (75.0)	20 (27.8)	114 (26.8)	45 (36.9)	6 (25.0)
Anxiety	9 (6.9)	38 (4.5)	2 (0.8)	0	2 (2.7)	29 (9.6)	0	0	2 (2.8)	12 (2.8)	0	0
Tremor	29 (22.3)	142 (16.6)	37 (14.0)	4 (13.3)	12 (16.0)	64 (21.1)	15 (14.7)	2 (25.0)	9 (12.5)	36 (8.5)	11 (9.0)	2 (8.3)
Overall Respiratory Events	77 (22.3)	489 (57.3)	157 (59.5)	16 (53.3)	12 (16.0)	163 (53.8)	56 (54.9)	6 (75.0)	9 (12.5)	150 (35.2)	35 (28.7)	3 (12.5)
Bronchitis	5 (3.8)	38 (4.5)	16 (6.1)	2 (6.7)	3 (4.0)	10 (3.3)	3 (2.9)	1 (12.5)	1 (1.4)	21 (4.9)	4 (3.3)	0
Respiratory disorder	9 (6.9)	45 (5.3)	10 (3.8)	1 (3.3)	11 (14.7)	22 (7.3)	7 (6.9)	1 (12.5)	1 (1.4)	8 (1.9)	2 (1.6)	0
Sinusitis	10 (7.7)	43 (5.0)	12 (4.5)	0	12 (16.0)	24 (7.9)	5 (4.9)	0	5 (6.9)	9 (2.1)	1 (0.8)	0
Overall Urogenital Events	10 (7.7)	90 (10.6)	29 (11.0)	5 (16.7)	8 (10.7)	36 (11.9)	14 (13.7)	0	14 (9.4)	50 (11.7)	9 (7.4)	5 (20.8)

Source: Applicant's Table 4.1.3.1.2, Section 2.7.4

The following observations are drawn from the above table regarding Type 2 patient adverse events and age:

- Small numbers of patients age ≥ 75 years make interpretation of event rates difficult in this age group.
- Rates of accidental injury were approximately equal between Type 2 inhaled insulin and SQ patients for those ages 18-44 years. In the inhaled insulin group, this declined with increasing age, while with SQ insulin, accidental injury increased with age. No age pattern was noted for accidental injury for OA patients.
- For inhaled insulin patients, there was a decline in the incidence of nausea and "respiratory disorder" by age group; this pattern was not seen for SQ or OA patients.
- For inhaled insulin patients, the incidence of hypoglycemia reported as an adverse event increased with age, while for SQ patients, the incidence was equal between age groups. However, the incidence for each age group was always higher for SQ patients than for inhaled insulin patients, and the incidence for oral agent patients was always much lower than that seen with either insulin treatment.
- The incidence of respiratory adverse events appeared to increase with age in all treatment groups. For each age group, the incidence among inhaled insulin patients was always higher than that seen in either comparator group, with the exception of those patients ≥ age 75 years, where small patient numbers make interpretation difficult.
- The incidence of bronchitis appeared to increase with age for inhaled insulin group patients; this pattern was not seen for comparator agents

- The incidence of sinusitis appeared to decline with age for all treatment groups.
- Overall urogenital events appeared to increase with age for all treatment groups.

Table 7.4.2.3.5 Additional Events with Possible Relationship to Gender for Type 1 Diabetic Inhaled Insulin Patients, Controlled Phase 2/3 Trials

	Male	Female	Male	Female
Adverse Event	**Inh Ins N=390 n (%)**	**Inh Ins N=308 n (%)**	**SQ N=385 n (%)**	**SQ N=320 n (%)**
Accidental injury	15 (13.3)	25 (8.1)	46 (11.9)	34 (10.6)
Allergic Reaction	20 (5.1)	11 (3.6)	10 (2.6)	13 (4.1)
Headache	49 (12.6)	56 (18.2)	41 (10.6)	69 (21.6)
Overall Digestive Events	112 (28.7)	122 (39.6)	83 (21.6)	119 (37.2)
Diarrhea	33 (8.5)	17 (5.5)	9 (2.3)	26 (8.1)
Gastroenteritis	15 (3.8)	19 (6.2)	19 (4.9)	17 (5.3)
Nausea	19 (4.9)	39 (12.9)	10 (2.6)	36 (11.3)
Vomiting	14 (3.6)	19 (6.2)	5 (1.3)	21 (6.6)
Overall Hemic and Lymphatic Events	8 (2.1)	10 (3.2)	12 (3.1)	16 (5.0)
Arthralgia	19 (4.9)	24 (7.8)	17 (4.4)	15 (4.7)
Overall Nervous System Events	112 (28.7)	145 (47.1)	127 (33.0)	141 (44.1)
Anxiety	17 (4.4)	32 (10.4)	14 (3.6)	25 (7.8)
Dizziness	22 (5.6)	36 (11.7)	27 (7.0)	24 (7.5)
Insomnia	9 (2.3)	14 (4.5)	2 (0.5)	12 (3.8)
Tremor	43 (11.0)	79 (25.6)	52 (13.5)	75 (23.4)
Overall Respiratory Events	276 (70.8)	239 (77.6)	219 (56.9)	209 (65.3)
Dyspnea	11 (2.8)	16 (5.2)	1 (0.3)	3 (0.9)
Pharyngitis	60 (15.4)	63 (20.5)	44 (11.4)	59 (18.4)
Respiratory disorder	19 (4.9)	26 (8.4)	14 (3.6)	13 (4.1)
Sinusitis	26 (6.7)	38 (12.3)	16 (4.2)	32 (10.0)
Sweating	22 (5.6)	38 (12.3)	39 (10.1)	35 (10.9)
Overall Urogenital Events	18 (4.6)	61 (19.8)	13 (3.4)	71 (22.2)
Urinary tract infection	3 (0.8)	20 (6.5)	2 (0.5)	29 (9.1)
Source: Applicant's Table 4.1.4.1.1, Section 2.7.4				

The following adverse events occurred with higher frequency in males than in females in the inhaled insulin group, but not in the SQ group: allergic reaction, diarrhea.

The following adverse event occurred with higher frequency in males than in females in both treatment groups: accidental injury.

The following adverse events occurred with higher frequency in females than in males in both treatment groups: headache, overall digestive events, gastroenteritis, nausea, vomiting, overall hemic and lymphatic events, arthralgia, overall nervous system disorders, dizziness, insomnia, tremor, overall respiratory events, dyspnea, pharyngitis, respiratory disorder, sinusitis, sweating, overall urogenital events, urinary tract infection.

Table 7.4.2.3.6 Additional Events with Possible Relationship to Gender for Type 2 Diabetic Inhaled Insulin Patients, Controlled Phase 2/3 Trials

	Inh Ins		SQ		OA	
Adverse Event	**Male N=795 n (%)**	**Female N=482 n (%)**	**Male N=307 n (%)**	**Female N=181 n (%)**	**Male N=361 n (%)**	**Female N=283 n (%)**
Accidental injury	73 (9.2)	25 (5.2)	32 (10.4)	23 (12.7)	21 (5.8)	20 (7.1)
Back pain	47 (5.9)	50 (10.4)	25 (8.1)	28 (15.5)	16 (4.4)	24 (8.5)
Pain	43 (5.4)	46 (9.5)	22 (7.2)	18 (9.9)	14 (3.9)	21 (7.4)
Headache	79 (9.9)	85 (17.6)	13 (4.2)	20 (11.0)	32 (8.9)	35 (12.4)
Overall Digestive Events	231 (29.1)	162 (33.6)	68 (22.1)	67 (37.0)	98 (27.1)	96 (33.9)
Diarrhea	50 (6.3)	38 (7.9)	16 (6.3)	12 (6.6)	28 (7.8)	40 (14.1)
Nausea	33 (4.2)	46 (9.5)	15 (4.9)	10 (5.5)	12 (3.3)	21 (7.4)
Vomiting	12 (1.5)	20 (4.1)	8 (2.6)	7 (3.9)	10 (2.8)	13 (4.6)
Hypoglycemia	517 (65.0)	277 (57.5)	222 (72.3)	138 (76.2)	105 (29.1)	80 (28.3)
Arthralgia	46 (5.8)	38 (7.9)	24 (7.8)	17 (9.4)	15 (4.2)	24 (8.5)
Anxiety	25 (3.1)	28 (5.8)	11 (3.6)	22 (12.2)	5 (1.4)	10 (3.5)
Paresthesia	29 (3.6)	26 (5.4)	6 (2.0)	2 (1.1)	14 (3.9)	5 (1.8)
Bronchitis	31 (3.9)	30 (6.2)	10 (3.3)	7 (3.9)	11 (3.0)	15 (5.3)
Respiratory disorder	46 (5.8)	19 (3.9)	26 (8.5)	15 (8.3)	7 (1.9)	4 (1.4)
Respiratory tract infection	232 (29.2)	125 (25.9)	102 (33.2)	64 (35.4)	69 (19.1)	58 (20.5)
Sinusitis	30 (3.8)	35 (7.3)	21 (6.8)	20 (11.0)	3 (0.8)	12 (4.2)
Rash	27 (3.4)	24 (5.0)	10 (3.3)	11 (6.1)	3 (0.8)	10 (3.5)
Urinary tract infection	10 (1.3)	40 (8.3)	6 (2.0)	19 (10.5)	5 (1.4)	19 (6.7)

Source: Applicant's Table 4.1.4.1.2, Section 2.7.4

The following adverse events occurred with higher frequency in males than in females in the inhaled insulin group, but not in the comparator groups: accidental injury, hypoglycemia, respiratory tract infection.

The following adverse event occurred with higher frequency in females than in males in the inhaled insulin group, but not in the comparator groups: paresthesia.

The following adverse events occurred with higher frequency in females than in males in all treatment groups: back pain, pain, headache, overall digestive events, diarrhea, nausea, vomiting, arthralgia, anxiety, bronchitis, respiratory disorder, sinusitis, rash, urinary tract infection.

A summary of the observations for demographic differences for adverse events includes:

- Numbers of non-Caucasian patients were too small to permit meaningful comparisons between treatment groups.
- For Type 1 patients, the event "sputum increased" had a higher incidence in older patients and in males in inhaled insulin patients, but not in SQ patients.
- For Type 1 patients in the SQ group, overall respiratory events occurred with decreasing frequency by age group, but in inhaled insulin patients, overall respiratory events occurred with approximately equal frequency between age groups. For patients age 18 and older, overall respiratory events occurred more frequently among inhaled insulin group patients than among SQ patients.

- For Type 1 diabetic children, otitis media occurred more frequently in inhaled insulin group children than in SQ group children. Otitis media occurred with low and approximately equal frequency in adult Type 1 patients in both treatment groups.
- For Type 1 patients, the events "allergic reaction" and "diarrhea" occurred with higher frequency among males than among females in the inhaled insulin group. This gender difference was not apparent in comparator groups.
- For Type 2 patients, the event "dry mouth" appeared to decrease in incidence with age in inhaled and oral agent groups, but not in the SQ group.
- For Type 2 patients, for all treatment groups, women were more likely to experience cough than men; for both genders, cough occurred much more frequently in inhaled insulin group patients than in comparator patients.
- For Type 2 patients, the incidence of bronchitis increased by age group for inhaled insulin patients, but not for comparator patients.
- For Type 2 patients, accidental injury, hypoglycemia, and respiratory tract infection occurred more frequently in men than in women in the inhaled insulin group. This gender difference was not observed in the comparator groups.
- For Type 2 patients, paresthesia occurred more frequently in women than in men in the inhaled insulin group. This gender difference was not observed in the comparator groups.

Among these observations, those most likely to have clinical significance include:
- Otitis media in children appears related to inhaled insulin treatment.
- The incidence of bronchitis appears to increase by age group for inhaled insulin patients, but not for comparator patients.
- For Type 2 patients, accidental injury and hypoglycemia appear to occur more frequently in men than in women taking inhaled insulin. This gender difference was not observed in the comparator groups.

7.4.2.4 Explorations for drug-disease interactions and other extrinsic factor interactions

Pharmacokinetic studies of inhaled insulin in hepatic and renal impairment were not submitted by the applicant.

Study 1005 compared inhaled insulin PK between healthy patients and those with COPD. Following administration of 3 mg of inhaled insulin, Cmax was greater (by up to 50%) in COPD patients than in healthy subjects. Tmax occurred 25-50 minutes earlier in COPD patients compared to normal subjects. Overall insulin exposure (AUC_{0-360}) was greater in COPD patients than in healthy subjects (by approximately 15%). Bioavailability of inhaled insulin was 11% in healthy controls compared to 23-25% in COPD patients. Please see Dr. Seymour's review for further discussion of the interaction between inhaled insulin and COPD.

As of 1 Sep 04, four patients with COPD had died; one of these was taking inhaled insulin and died of metastatic colon cancer. No asthma patients had died as of 1 Sep 04.

Hypoglycemia event rates did not differ between COPD and asthma patients, and those without these disorders, for either inhaled insulin or comparator patients. The following adverse events had an incidence of at least 2% greater in asthma or COPD patients than in patients without these disorders:

Table 7.4.2.4.1 Incidence of Adverse Events Occurring with Greater Frequency for Patients with Underlying Lung Disease (Retrospectively and Prospectively Identified), than in Patients without Underlying Lung Disease, Adults, Controlled Phase 2/3 Studies

	Inh Ins			Comparator		
Event	**With BL Asthma N=70 n (%)**	**With BL COPD N=80 n (%)**	**W/O BL Lung Dz N=1901 n (%)**	**With BL Asthma N=79 n (%)**	**With BL COPD N=78 n (%)**	**W/O BL Lung Dz N=1756 n (%)**
Asthenia	9 (12.9)	8 (10.0)	167 (8.8)	5 (6.3)	6 (7.7)	123 (7.0)
Chest pain	2 (2.9)	1 (1.3)	22 (1.2)	1 (1.3)	1 (1.3)	6 (0.3)
Hot flushes	2 (2.9)	0	5 (0.3)	0	1 (1.3)	6 (0.3)
Vasodilation	2 (2.9)	0	10 (0.5)	0	0	10 (0.6)
Nausea	4 (4.3)	0	44 (2.3)	1 (1.3)	2 (2.6)	28 (1.6)
Hypercholesterolemia	3 (4.3)	1 (1.3)	4 (0.2)	0	1 (1.3)	4 (0.2)
Peripheral edema	2 (2.9)	3 (3.8)	25 (1.3)	2 (2.5)	1 (1.3)	21 (1.2)
Arthralgia	3 (4.3)	1 (1.3)	17 (0.9)	0	3 (3.8)	26 (1.5)
Arthritis	0	3 (3.8)	17 (0.4)	0	3 (3.8)	13 (0.7)
Circumoral paresthesia	0	2 (2.5)	2 (0.1)	0	0	2 (0.1)
Paresthesia	2 (2.9)	0	28 (1.5)	1 (1.3)	0	15 (0.9)
Bronchitis	1 (1.4)	2 (2.5)	9 (0.5)	0	1 (1.3)	0
Cough increased	4 (5.7)	8 (10.0)	290 (15.3)	1 (1.3)	1 (1.3)	18 (1.0)
Dyspnea	2 (2.9)	1 (1.3)	27 (1.4)	0	2 (2.6)	6 (0.3)
Respiratory disorder	0	2 (2.5)	23 (1.2)	1 (1.3)	2 (2.6)	3 (0.2)
Respiratory tract infection	3 (4.3)	3 (3.8)	36 (1.9)	4 (5.1)	1 (1.3)	29 (1.7)
Epididymitis (males only)	1 (4.2)	0	0	0	0	0

Source: Applicant's Tables 13.4.8.1-13.4.8.3, Section 5.3.5.3.1

Patients with either asthma or COPD who were taking inhaled insulin appeared to experience asthenia more frequently than comparator patients (with or without underlying lung disease), and more frequently than inhaled insulin patients without underlying lung disease. Otherwise, the small number of each type of event within the underlying lung disease groups precludes meaningful conclusions regarding other types of events.

Declines in FEV1 and DLco occurred more frequently among inhaled insulin patients than among control patients in the controlled Phase 2/3 population, and are further discussed in Dr. Seymour's pulmonary review. The clinical reviewer examined nonpulmonary adverse events in those patients who had significant declines in PFTs, defined as declines from baseline to last observation of ≥ 15% in FEV1, TLC or FVC, and/or ≥ 20% decline in DLco. Hypoglycemia rates (by study definition of requirement for assistance, or value <36 mg/dL) were similar between patients who had significant PFT declines and those who did not, for both inhaled insulin and comparator patients. Hypoglycemia rates among patients who had declines in PFTs were similar between inhaled insulin and comparator patients (source: applicant's Table 17.12, Section 5.3.5.3.1). Reported adverse events of hypoglycemia occurred more commonly in inhaled insulin patients who had significant declines in PFTs than in comparator patients who had significant declines in PFTs [154/218 (70.6%) vs 86/154 (55.8%)], but at an equal rate to

that seen in comparator patients who did not have significant declines in PFTs (1069/1512, 70.7%). Total cardiovascular events occurred at a higher rate in inhaled insulin patients who had a significant decline in PFTs (45/218, 20.6%) than in comparator patients who had a significant decline in PFTs (26/154, 16.9%) and comparator patients who did not have a significant decline in PFTs (202/1512, 13.4%). No single cardiovascular event occurred at a significantly higher rate among inhaled insulin patients who had significant declines in PFTs.

Tobacco smoking within six months prior to randomization was an exclusion criterion for Phase 2/3 studies. In clinical pharmacology studies (005, 016, 1003, 1020), inhaled insulin pharmacokinetics and pharmacodynamics were significantly different in smokers. In nondiabetic and Type 2 diabetic smokers, Cmax, Tmax and AUC of inhaled insulin was 2-5 fold higher than that of nonsmokers. Smoking cessation led to a decline in insulin exposure within 3 days of abstinence, with further attenuation over time; by 7 days, insulin exposure was near that seen in nonsmokers. Resumption of smoking after abstinence resulted, within 2-3 days, in increased exposure similar to that seen prior to smoking cessation. The applicant is concerned about these findings, and considers the potential for rapid changes in systemic insulin exposure to be a prohibitive risk associated with cigarette smoking. The applicant recommends that patients should abstain from smoking for at least 6 months before inhaled insulin treatment, and should remain abstinent during inhaled insulin treatment. However, in order to reduce the likelihood that smokers will use inhaled insulin, education of patients and providers may be needed, with enhanced emphasis on the risk. Physicians may overlook the smoking statement in a long product label, and patients sometimes do not share their smoking history with their physicians.

The applicant conducted a rhinoviral challenge study, in which volunteers were inoculated with either rhinovirus or saline. Among those rhinovirally challenged patients who developed a cold, insulin Cmax was numerically greater than it was among saline group patients who did not develop a cold, although this difference was not statistically significant. On Day 4, Tmax was statistically significantly longer in patients who developed a cold.

Table 7.4.2.4.2 Insulin Pharmacokinetic Parameters after Rhinoviral Challenge, Study 010

Summary of Statistical Analysis of Pharmacokinetic Parameters

Parameter	Day	Adjusted Geometric Means*			Cold vs Virus No Cold		Cold vs Saline	
		Cold	Virus No Cold	Saline	Adjusted Ratio * (90% CI)	p-value	Adjusted Ratio * (90% CI)	p-value
AUC (µU.min/mL)	3	703	1209	455	0.58 (0.33, 1.04)	0.1218	1.55 (0.76, 3.14)	0.3010
	4	692	584	782	1.19 (0.57, 2.48)	0.6940	0.89 (0.36, 2.19)	0.8186
Cmax (µU/mL)	3	11.88	13.58	6.48	0.88 (0.48, 1.61)	0.7083	1.83 (0.85, 3.97)	0.1895
	4	11.27	7.71	8.18	1.46 (0.80, 2.66)	0.2856	1.38 (0.64, 2.94)	0.4741
	Day	Arithmetic Means			Cold vs Virus No Cold		Cold vs Saline	
		Cold	Virus No Cold	Saline	Estimated Difference (90% CI)	p-value	Estimated Difference (90% CI)	p-value
Tmax (min)	3	35.8	40.7	33.8	-4.9 (-19.8, 9.9)	0.5718	2.0 (-16.0, 20.1)	0.8494
	4	47.3	50.0	22.5	-2.7 (-15.9, 10.5)	0.7287	24.8 (8.7, 40.9)	0.0148

* For AUC and Cmax the Day 1 log (AUC) or log (Cmax) was used as a covariate in the model. CI = confidence interval
Day 1: Before inoculation; Days 3 and 4: Post-inoculation

Source: Applicant's Study 010 report, pg 9

Glucose Cmax was higher on days 3 and 4 after rhinoviral inoculation than after saline inoculation. AUC was also higher, but baseline differences limit the interpretability of this finding.

Table 7.4.2.4.3 Glucose Pharmacodynamic Parameters with Rhinoviral Challenge, Study 010

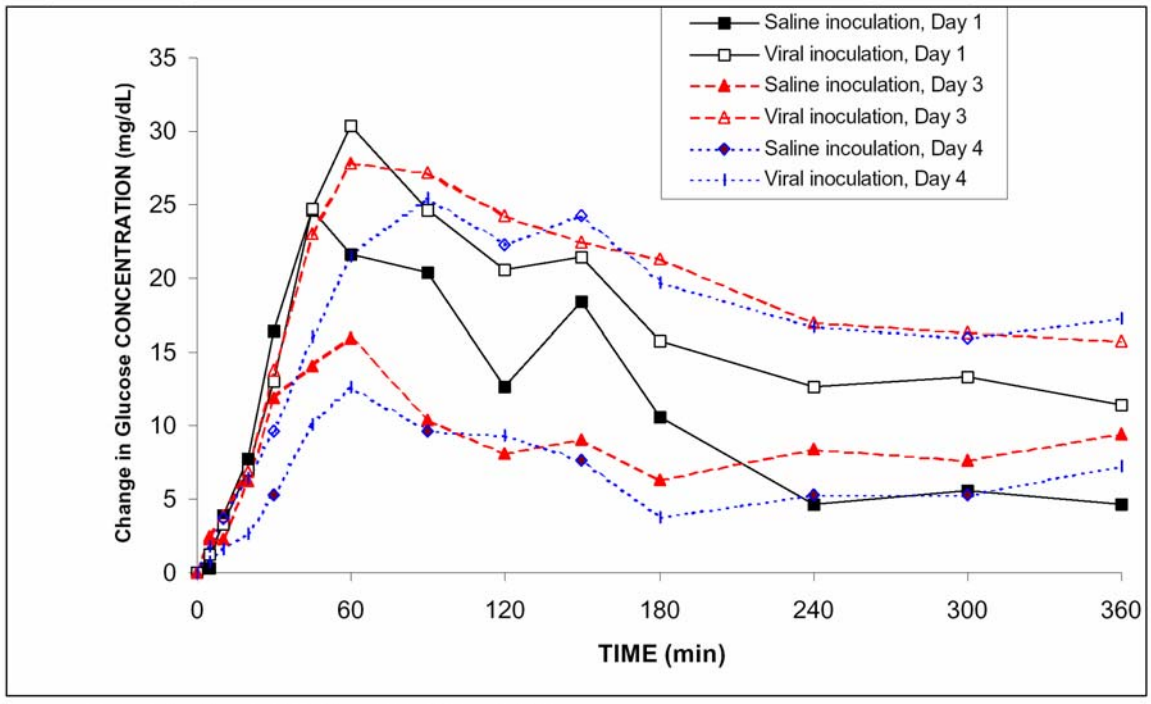
Arithmetic Mean (CV%) of Glucose Pharmacodynamic Parameters

	Virus (N=20)			Saline (N=4)		
	Day 1	Day 3	Day 4	Day 1	Day 3	Day 4
AUC0-360 (mg·min/mL)	5830 (47)	6900 (49)	6460 (47)	3930 (53)	3150 (53)	2370 (34)
Cmax (mg/dL)	33.2 (35)	31.4 (43)	29.2 (45)	28.4 (74)	18.6 (59)	16.1 (65)
Tmax (min)	75.0 (77)	81.0 (43)	136 (66)	75.0 (67)	165 (86)	120 (71)

Day 1: Before inoculation; Days 3 and 4: Post-inoculation
Source: Table 5.4.1-5.4.3

Figure 7.4.2.4.1 Mean Glucose Concentrations over Time, After Rhinoviral Challenge, Study 010

Inhaled Human Insulin Protocol 010
Mean Change in Glucose Concentrations Following Administration of 3 mg Inhaled Insulin to Subjects on Days 1, 3 and 4 with Nasal Inoculation 6 Hours After Dosing on Day 1



Source Data: Section 13, Tables 2.4, 2.5 and 2.6

Source: Applicant's Figure 1.4, Study 010 report

The applicant's proposed label states that Exubera® may be used during intercurrent respiratory illness. The absence of a significant difference in insulin Cmax after rhinoviral infection is a

useful finding, but rhinoviral challenge does not cover the spectrum of intercurrent respiratory illness.

7.4.2.5 Explorations for drug-drug interactions

Study 1005 included pharmacokinetic data regarding co-administration of inhaled insulin and inhaled albuterol. While overall, inhaled insulin PK did not differ from 30 minutes pre- to 30 minutes post- albuterol, the small subset of emphysema patients (5/12 total COPD patients) had mean insulin exposure that was 46% higher post-albuterol than pre-albuterol.

No other specific drug interaction studies were reported.

7.4.3 Causality Determination

The following adverse events appear to have a causal relationship to inhaled insulin use:

- serious hypoglycemia in intensively treated Type 1 diabetics (by the applicant's analysis; FDA biostatistics reanalysis indicates there may be no difference between treatment groups)
- cough in Type 1 adult, Type 2 adult, and Type 1 child patients
- declines in pulmonary function tests (FEV1 and DLco) in Type 1 and Type 2 adults
- rhinitis, pharyngitis and sinusitis in Type 1 and Type 2 adults
- otitis media and other ear events in Type 1 children

Other respiratory adverse events which may have a causal relationship to inhaled insulin are discussed in the pulmonary safety review.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

In the DOSAGE AND ADMINISTRATION section of the proposed product label, the applicant proposes a similar regimen to that used in clinical trials. Administration 10 minutes prior to meals is proposed. Calculation of initial dosage based on body weight is proposed, with a formula: body weight (kg) x 0.05 mg, rounded down to nearest whole mg, = premeal dose, assuming 3 meals/day. The applicant does not propose instructions for transitioning from subcutaneous premeal insulin to inhaled insulin, based on the patient's current premeal subcutaneous insulin dose. No formula is presented for dosing by carbohydrate exchanges, and there are no recommendations for calculation of bedtime snack doses. The label does not include recommendations for titration increments. Mention is made of the fact that three 1 mg unit dose blisters cause greater insulin exposure than one 3 mg dose blister. The dosage and administration section does not mention a need for close monitoring by the patient and physician during initiation of inhaled insulin.

Initial dosage based on body weight is a reasonable approach. However, numerous patient factors may affect initial inhaled insulin requirement, including the patient's particular degree of insulin resistance, current glycemic control, hypoglycemia history, et al. These factors could result in significant under- or over- dosing if initial dose is based on weight alone. The proposed label makes mention of the need for consideration of factors other than weight in determining starting dose, but does not provide specific guidance. The potential consequences of initial under- or over- dosing could likely be managed by intensive monitoring by the patient and physician in the first few weeks of initiation of inhaled insulin; the clinical reviewer recommends the addition of this recommendation to the product label.

The applicant's proposed label states, in the DOSAGE AND ADMINISTRATION section, that Exubera® may be used during intercurrent respiratory illness, e.g. bronchitis, upper respiratory infection, and rhinitis. However, some differences in inhaled insulin pharmacokinetics and glucose pharmacodynamics were seen with rhinoviral challenge. Analysis of the effect of acute bronchitis on insulin pharmacokinetics and post-inhaled-insulin glucose pharmacodynamics was not provided. The clinical reviewer recommends that the label state that the effect of intercurrent respiratory illness, such as acute bronchitis, upper respiratory infection, and rhinitis, has not been fully evaluated, and that careful monitoring of blood glucose during intercurrent respiratory illness is recommended. The clinical reviewer also recommends that patients be advised to have subcutaneous insulin and needles available for use during intercurrent respiratory illness, in case glucose control proves difficult with inhaled insulin during that time.

An important consideration in dosage titration is lack of dose bioequivalence, i.e. the fact that insulin Cmax and AUC are higher if one uses three 1-mg blisters than if one uses a single 3-mg blister. In Study 1006, the applicant compared (in healthy subjects) the PK of 3x1 mg and 1x3 mg, as presented in the following table.

Table 8.1.1 Comparison of Insulin Pharmacokinetics with Administration of 3x1 mg and 1x3 mg Inhaled Insulin Blisters in Healthy Volunteers, Study 1006

Statistical Analysis of Insulin Pharmacokinetic Parameter Means

Parameter	3x1 mg*	1x3 mg*	Ratio/Difference	90% CI
$AUC_{0\text{-}360}$ (μU·min/mL)	2599	1859	140%	(117%, 167%)
Cmax (μU/mL)	31.02	24.51	127%	(108%, 148%)
F (%)**	5.80	4.15	140%	(117%, 167%)
Tmax (min)	44.4	42.0	2.4	(-4.4, 9.2)

*Adjusted geometric means for AUC, Cmax, and F; adjusted arithmetic mean for Tmax
**AUCinhaled/AUCsc; calculated from dose-standardized AUCs

Applicant used statistical F-distribution to compute 95% CI for ratio
Source: Study 1006 report, pg 7

Please see the Human Biopharmacology review for a more complete discussion of Study 1006; that review is ongoing as of 4 Aug 05, but will represent the most accurate FDA interpretation of clinical pharmacology data. Because this study was conducted in nondiabetic subjects, the potential glucodynamic effects of this difference in PK cannot be precisely predicted. However, in these nondiabetic volunteers, mean changes in glucose concentration and AUC were greater

with 3x1 mg than with 1x3 mg. The applicant includes information regarding this finding in the DOSAGE AND ADMINISTRATION section, and states that 1x3 mg cannot be substituted for 3x1 mg; however, the potential implications for titration are not presented. A potential problem exists when titrating dose up to a multiple of three mg from a dose that is one mg below that multiple, e.g. titration from 2-3 mg, from 5-6 mg, or from 8-9 mg. One can predict with reasonable certainty that the incremental increase in serum insulin concentration, and the incremental decrease in blood glucose, will be less when one titrates from 2-3 mg (or 5-6 mg) than it was when the patient was titrated from 1-2 mg (or 4-5 mg). If the serum insulin concentration can be predicted to always be greater at 1x3 mg than at 2x1 mg, and the blood glucose concentration can be predicted to always be lower after 1x3 mg than after 2x1 mg, then titration can occur safely and without the need for complicated titration instructions. However, the magnitude of the difference in serum insulin AUC_{0-360} between 3x1 mg and 1x3 mg is large, with a ratio of 140% (90% CI 117%, 167%). This implies that some patients could have lower insulin levels after titration to 1x3 mg than they had before titration at 2x1 mg. For example, assuming that each 1 mg blister inhalation resulted in an equal increase in insulin concentration, one would see the following AUC_{0-360}s:

1x1 mg = appr 866 μU-min/mL
2x1 mg = appr 1733 μU-min/mL
3x1 mg = 2599 μU-min/mL

Under this scenario of the mean values with a ratio of 140%, a patient who was taking 2x1 mg blisters would have an increase in insulin AUC_{0-360} when going from 2x1 mg to 1x3 mg (appr 1733 μU-min/mL to 1859 μU-min/mL). However, if the ratio was at the upper limit of the 90% CI, i.e. 167%, the following would result:

2599/1859 = 140/100
2599/n = 167/100; n = 1556 μU-min/mL for the insulin AUC_{0-360} achieved with 1x3 mg (when the ratio is at the upper limit of the 90% CI)

Therefore, a patient going from 2x1 mg to 1x3 mg apparently could have a paradoxic decline in serum insulin AUC_{0-360}, from appr 1733 μU-min/mL to appr 1556 μU-min/mL.

When looking at this same question using a fixed value for the insulin AUC_{0-360} for 1x3 mg, and assuming the value for 3x1 mg was 167% of that (the upper limit of the 90% CI), one gets the following:

1859/2599 = 100/140
1859/n = 100/167, n = 3104 μU-min/mL for the insulin AUC_{0-360} achieved with 3x1 mg (when the ratio is at the upper limit of the 90% CI)

Again assuming that each 1 mg blister inhalation resulted in an equal increase in insulin AUC, one would see the following AUC_{0-360}s:

1x1 mg = appr 1035 mg

2x1 mg = appr 2070 mg
3x1 mg = appr 3104 mg

In this case, once again, a patient going from 2x1 mg to 1x3 mg apparently could have a paradoxic decline in serum insulin, from approximately 2070 µU-min/mL to approximately 1859 µU-min/mL.

These calculations extrapolate from percentages, and can only be used to give a rough idea of the possibility of titration problems related to the difference between 3x1 mg and 1x3 mg.

Study A2171012, a dose proportionality study, provides further concerns regarding potential problems with titration. In this study, dose proportionality was not demonstrated over a range of doses. Dose proportionality of several dosages was compared, including doses of 1 mg (1x1 mg), 2 mg (2x1 mg), 3 mg (1x3 mg), 4 mg (1x3 mg + 1x1 mg) and 6 mg (2x3 mg). None of the 90% confidence intervals for any AUC comparison fell within bioequivalence boundaries (80-125%).

When examining the actual individual subject data from the trial, one notes that multiple samples obtained for insulin Cmax and AUC for 3 mg dosing had lower values than the mean seen for 2 mg dosing. For Cmax, 10/29 samples obtained for Cmax at the 3 mg dose fell below the mean Cmax for the 2 mg dose. In this study, each patient generally only received 3 of the 5 dose combinations. A total of 6 patients received both the 2 mg dose and the 3 mg dose (doses given at different times during study). Among these 6 patients (each of whom had 2 Cmax values recorded for each dose), 4/6 had a Cmax value for the 3 mg dose that was lower than a Cmax value for the 2 mg dose. A total of 6/26 samples for the 6 mg dose had lower Cmax values than the mean for the 4 mg dose, and 2/6 patients who received both the 4 mg dose and the 6 mg dose had a Cmax value for the 6 mg dose that was lower than a Cmax value for the 4 mg dose.

Similar findings are noted for AUC at each time interval, as illustrated in the following table:

Table 8.1.2 Overlap of Insulin AUC Values Between 2 mg and 3 mg Inhaled Insulin Doses, Study A2171012

	AUC 0-60	AUC 0-120	AUC 0-360	AUC 0-600
Number and percentage of AUC samples for 3 mg dose with lower AUC then the mean AUC for the 2 mg dose	8/29 (28%)	9/29 (31%)	8/29 (28%)	10/29 (34%)
Number and percentage of AUC samples for 6 mg dose with lower AUC then the mean AUC for the 4 mg dose	6/26 (23%)	4/26 (15%)	6/26 (23%)	7/26 (27%)
Number and percentage of patients who had both a 3 mg and 2 mg dose, who had a lower AUC value at the 3 mg dose than a 2 mg dose AUC[1]	4/6 (67%)	2/6 (33%)	2/6 (33%)	3/5 (60%)
Number and percentage of patients who had both a 6 mg and 4 mg dose, who had a lower AUC value at the 6 mg dose than a 4 mg dose AUC	4/6 (67%)	2/6 (33%)	2/6 (33%)	2/6 (33%)

1 Each patient had two measurements for each AUC time interval.

Based on these studies, it appears that the possibility exists that, in a given patient, the titrated "increase" from 2x1 mg to 1x3 mg could actually result in lower blood insulin AUC, rather than the expected increase in blood insulin. This could create a significant problem in upward titration of dose, particularly in the lower dosage ranges such as might be used in Type 1

diabetes. This problem would be magnified if the drug is used off-label for the treatment of pediatric Type 1 diabetics, who generally have lower body weights and therefore smaller initial insulin doses.

Furthermore, patients must be strongly cautioned that if they run out of 3 mg blisters, they must not substitute three 1 mg blisters for each 3 mg blister, because of the risk of severe hypoglycemia.

In order to search for a clinical correlate for these problems with dose proportionality and dose equivalence, the clinical reviewer examined all narratives for serious adverse events of hypoglycemia. A possible indication of a clinical correlate would be a finding that a disproportionate number of serious hypoglycemic events were preceded by a dose of 3x mg + 1 mg, e.g. 4 mg, 7 mg, 10 mg, etc. This could occur if the increase in insulin concentration was unexpectedly large when a patient was titrated from a dose requiring only 3 mg blisters to a dose requiring 3 mg blisters plus a one mg blister. However, doses of 4, 7 or 10 mg did not occur in a disproportionately high number of patients; such doses were given prior to the hypoglycemic event for only 7/47 episodes for which inhaled insulin dose data were available.

Table 8.1.3 Serious Hypoglycemic Adverse Events: Time of Event, Last Inhaled Insulin Dose Prior to Event, and Accompanying Related Events

Pt ID	Pt Age	Time of Day of Hypoglycemic Event	Last Inhaled Insulin Dose Prior to Event	Accompanying Related Event(s)
1009-5088-3381	7	after lunch	2 mg prelunch	fall, unresponsiveness
1009-5096-3021	10	0429	not in narrative	confusion, lethargy, possible seizure
1022-1001-0009	37	0445	3 mg at 1930 previous night	unconsciousness
1022-1015-0837	37	0430	4 mg presupper previous night	loss of consciousness
1022-1025-1424	32	0630 (prebreakfast)	not in narrative	confusion, change in affect
1022-1026-1489	22	0715 (prebreakfast)	7 mg at 1930 previous night	disorientation, motor vehicle accident
1002-1037-2136	51	0620	1 mg at 0120	loss of consciousness
1022-1029-1661	35	0530	7 mg at 2030 previous night	difficult to arouse
1022-1050-3914	46	1930 (postsupper)	3 mg at 1800 (presupper)	disorientation
		0630	7 mg presupper previous night	incoherence
		0500	8 mg at 1900 previous night	incoherence
1022-5074-3082	51	0230	12 mg presupper previous night	to ER for "hypoglycemic symptoms"
1022-5147-3376	45	0626	6 mg presupper previous night	disorientation, memory loss
		0538	6 mg presupper previous night	disorientation, memory loss
		0530-0630	6 mg presupper previous night	disorientation, memory loss
1026-1001-0017	50	0420	1 mg at 2310 previous night	semiconsciousness, unresponsiveness
1027-5148-1329	43	2105	6 mg presupper	loss of consciousness
1029-1059-2607	45	postbreakfast	4 mg prebreakfast	seizure
1029-1093-	64	2200	4 mg at 1730	unconsciousness

Table 8.1.3 Serious Hypoglycemic Adverse Events: Time of Event, Last Inhaled Insulin Dose Prior to Event, and Accompanying Related Events

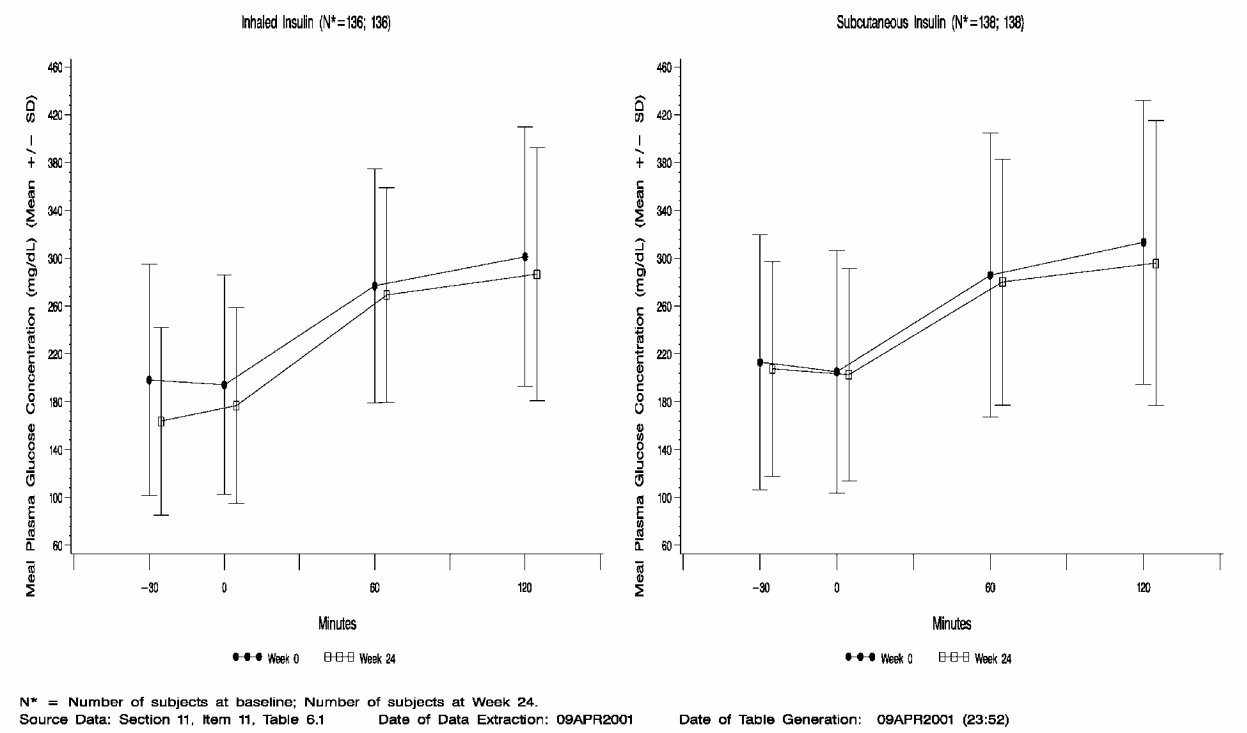
Pt ID	Pt Age	Time of Day of Hypoglycemic Event	Last Inhaled Insulin Dose Prior to Event	Accompanying Related Event(s)
3854				
		2122	3 mg at 1830	unconsciousness
1029-1093-3857	62	postlunch	not in narrative	loss of consciousness
		between 1400 and 1600	not in narrative	not in narrative; EMS treated
106-5025-6592	42	postbreakfast	not in narrative	confusion, possible seizure
		0700	6 mg at 0140	convulsions
		0540	not in narrative	seizure, tongue-biting
106-5030-6883	53	0900	not in narrative	found unconscious; hypothermia
		1800	3 mg prelunch	found in car by side of road; sluggish speech
		prelunch	6 mg prebreakfast	unresponsiveness
106-5060-6966	36	early morning	not in narrative	unresponsiveness
		early morning	not in narrative	coma
107-5052-7181	19	0850	dose not in narrative; last inh ins 9.5 hrs prior to event	difficult to arouse
		0900	dose not in narrative; last inh ins 10.5 hrs prior to event	difficult to arouse
		0604	dose not in narrative; last inh ins 9 hrs prior to event	difficult to arouse
		0525	dose not in narrative; last inh ins 9 hrs prior to event	difficult to arouse
		0858	dose not in narrative; last inh ins 11.5 hrs prior to event	difficult to arouse
		0758	dose not in narrative; last inh ins 12 hrs prior to event	difficult to arouse
		0530	dose not in narrative; last inh ins 9 hrs prior to event	difficult to arouse
		0600	dose not in narrative; last inh ins 8 hrs prior to event	difficult to arouse
		0625	dose not in narrative; last inh ins 12 hrs prior to event	difficult to arouse
107-5052-7181	53	midnight	not in narrative	ran his car into a ditch
107-5083-7499	17	afternoon	1 mg prior to lunch	
107-5127-7221	30	morning	not in narrative	seizure
		2200	6 mg presupper	seizure
		after bedtime	6 mg presupper	seizure
		0400	6 mg presupper	seizure
		after bedtime	6 mg presupper	seizure
		0400	not in narrative	seizure
109-5071-0483	66	1900	6 mg at 1800	unresponsiveness
111-5017-8450	73	1630	5 mg prelunch	car crash, disorientation, confusion
111-5052-7180	34	early morning	3 mg presupper	incoherent speech, crying
111-5061-7793	44	1800	8 mg presupper	unconsciousness
111-5061-7794	31	0200	not in narrative	unconsciousness, incontinence
		0445	1 mg at 2215 previous night	disorientation
111-5061-7797	46	0300	2 mg at bedtime previous night	unconsciousness, fall

Table 8.1.3 Serious Hypoglycemic Adverse Events: Time of Event, Last Inhaled Insulin Dose Prior to Event, and Accompanying Related Events

Pt ID	Pt Age	Time of Day of Hypoglycemic Event	Last Inhaled Insulin Dose Prior to Event	Accompanying Related Event(s)
111-5066-7741	41	0230	dose not in narrative; last inh ins 6 hr prior to event	incoherence
111-5066-7745	29	0400	not in narrative	seizure
111-5070-6896	30	prebreakfast	9 mg presupper previous night	unresponsiveness
111-5070-6898	42	0030	2 mg presupper previous night	convulsions
111-5081-6446	18	1600	dose not in narrative; presupper previous night	incoherence
111-5082-3341	11	prebreakfast	not in narrative	seizure
111-5082-3346	10	prebed	7 mg presupper	
111-5082-3347	8	1300 (prelunch)	6 mg prebreakfast (ate at 0920)	seizure
111-5082-3348	9	1800	15 mg prelunch	confusion, unilateral leg weakness
		0100	12 mg presupper previous night	unresponsiveness
		early morning	not in narrative	possible seizure
111-5087-7011	17	0900	3 mg prebreakfast	confusion, disorientation
111-5088-3384	7	0240	3 mg at 2115 previous night	seizure
111-5091-3008	11	midnight	4 mg at 2200 previous night	seizure
111-5094-7094	14	0700	3 mg at 2200 previous night	incoherence, combativeness
111-5095-3334	7	2100	not in narrative	
111-5096-3358	12	0900	3 mg at 1800 previous night	confusion
111-5096-3359	10	0500	1 mg at 2152 previous night	seizure
111-5098-3048	9	0600	3 mg at 2048 previous night	seizure
		0615	2 mg at 2005 previous night	seizure
111-5127-7224	60	1800	3 mg prelunch	unconsciousness

As discussed above, and in Sections 3.1 and 5.1, concerns exist on several levels regarding the potential for variability in delivered dose of insulin. However, significant variability in delivered dose of insulin and, more importantly, in pharmacodynamic effect, is also seen with subcutaneous insulin (Heinemann 2002). This marked variability in pharmacodynamic effect of injected insulin has been well-described in the medical literature, and represents a major barrier in efforts to achieve lower HbA1cs without undue risk of severe hypoglycemia. The relative variability of the pharmacodynamic effect for inhaled versus subcutaneous insulin can be compared using standardized meal study data from within the major trials of inhaled insulin that used subcutaneous insulin as a comparator. For example, in Study 107, patients received either inhaled insulin or subcutaneous insulin, followed by a standard Sustacal® meal. The following figures illustrate the plasma glucose response over time:

Figure 8.1 Meal Study Plasma Glucose Concentration (mg/mL), Study 107



Source: Applicant's Figure 4.1, Study 107 report

Of note from this figure is the fact that the standard deviations for plasma glucose following administration of a standard meal are large for patients who received inhaled insulin, but the standard deviations seen for those patients who received subcutaneous insulin are at least as large as those seen with inhaled insulin. Similar findings were seen in other studies where inhaled insulin was compared to subcutaneous insulin after a standardized meal. Thus, although concern exists regarding the variability seen with inhaled insulin, it may be no worse than that seen with subcutaneous insulin.

8.2 Drug-Drug Interactions

Study 1005 included pharmacokinetic data regarding co-administration of inhaled insulin and inhaled albuterol. While overall, inhaled insulin PK did not differ from 30 minutes pre- to 30 minutes post- albuterol, the small subset of emphysema patients (5/12 total COPD patients) had mean insulin exposure that was 46% higher post-albuterol than pre-albuterol.

No other specific drug interaction studies were reported.

8.3 Special Populations

Study 1004 was conducted in elderly (>65 years of age), obese Type 2 diabetics, and compared inhaled insulin (4 mg) PK and PD to that of SQ regular insulin (12 U) (6 mg inh ins or 18 U SQ for patients with weight ≥150 kg). The study did not include a control arm of younger patients.

Inhaled insulin had an earlier insulin Tmax and a higher Cmax, but a similar exposure by AUC_{0-360}.

Table 8.3.1 Glucose Pharmacodynamics for Inhaled and Subcutaneous Insulin in Patients >Age 65 years, Study 1004

Statistical Analysis of Geometric and Arithmetic Means for Inhaled and Subcutaneous Insulin Treatment

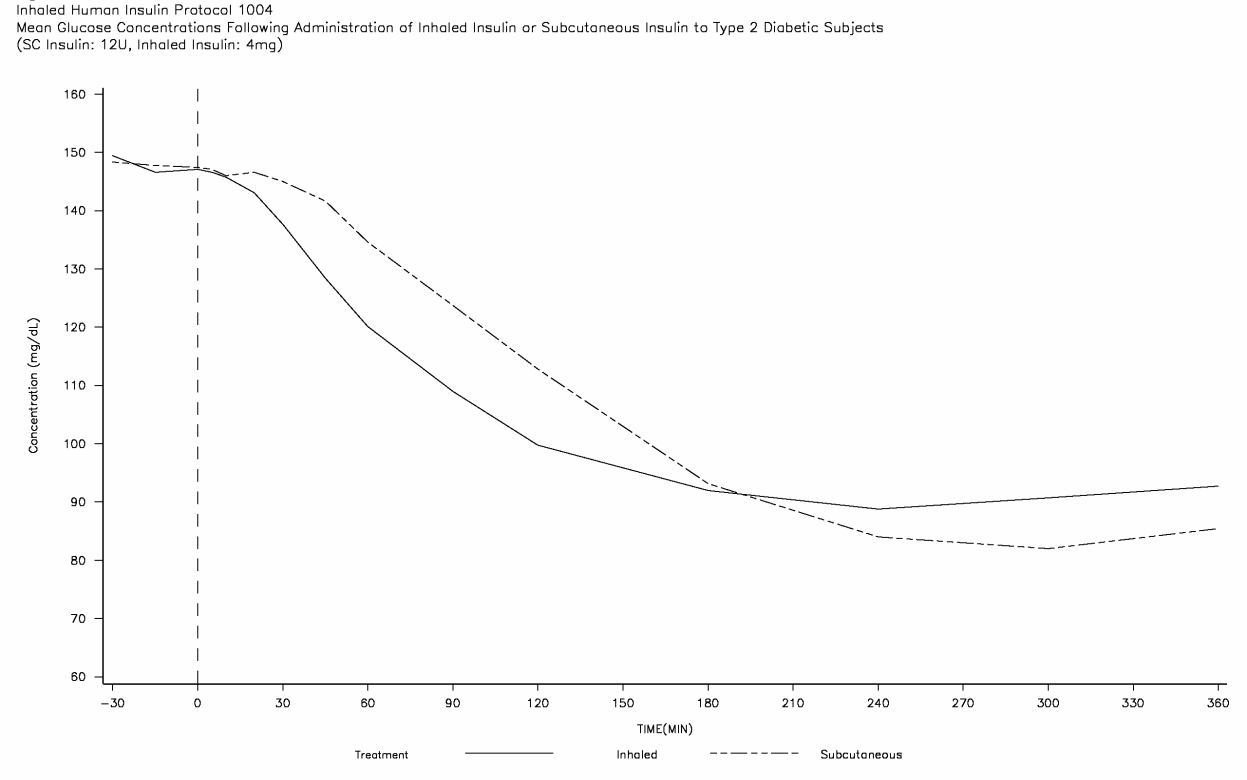
Pharmacokinetic Parameter	Adjusted Geometric Means		Ratio (%)	90 % Confidence Limits (%)
	INH	SC	(INH / SC)	
AUC_{0-120} (µU·min/mL)	3472	1852	187	(138, 255)
AUC_{0-240} (µU·min/mL)	4500	3937	114	(81, 161)
AUC_{0-360} (µU·min/mL)	4696	4823	97	(68, 139)
Cmax (µU/mL)	48.62	28.57	170	(131, 221)
	Adjusted Arithmetic Means		Difference (min)	(min)
Tmax (min)	37.6	99.6	-62.0	(-82.2, -41.8)

Source: Tables 5.3.1

Source: Applicant's Table 5.3.1, Study 1004 report

Decline in blood glucose concentrations was greater over the first 120 minutes after insulin administration for inhaled insulin than for SQ insulin.

Figure 8.3.1 Mean Glucose Concentrations Following Administration of Inhaled Insulin or Subcutaneous Insulin in Type 2 Diabetic Patients >65 Years of Age



Source: Applicant's Figure 2.1, pg 84, Study 1004 Report

The clinical reviewer was unable to find pharmacokinetic or pharmacodynamic data on the administration of equivalent mg/kg dosing of inhaled insulin to obese nonelderly Type 2 diabetics, and therefore cannot comment on the expected differences in PK/PD in elderly patients who receive inhaled insulin compared to younger patients who receive inhaled insulin. Because of the problems with nonequivalence of 1x3 mg and 3x1 mg, one cannot extrapolate PK/PD data from studies using other doses.

8.4 Pediatrics

Pediatric safety and efficacy data are presented in Sections 6 and 7 of this review. In each section, discussion of available pediatric data is presented after adult data.

8.5 Advisory Committee Meeting

This application is to be presented to the Endocrine and Metabolic Drugs Advisory Committee on 8 Sep 05.

8.6 Literature Review

Literature relevant to the review is referenced throughout the review.

8.7 Postmarketing Risk Management Plan

The applicant did not submit a postmarketing risk management plan that included measures other than routine postmarketing adverse event surveillance.

8.8 Other Relevant Materials

9 OVERALL ASSESSMENT

9.1 Conclusions

Conclusions reached in this review are the result of the clinical reviewer's evaluation of the clinical portions of the New Drug Application; nonclinical and clinical pharmacology portions are also under evaluation by reviewers with expertise in the relevant areas, and these reviews may also affect decisions made by signatory authorities regarding approvability of this application. A separate pulmonary clinical safety review is being conducted.

For each point of discussion in Section 9.1, the relevant section number for the main body of the review is included to permit ease of reference. If an entire paragraph contained information from a single section of the main body of the review, the relevant section number is included after the first sentence in the paragraph in Section 9.1.

9.1.1 Efficacy Conclusions

The applicant proposes the following language for the "Indications and Usage" section of the product label:

"EXUBERA is indicated for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia. EXUBERA has an onset of action similar to rapid-acting insulin analogs and has a duration of glucose-lowering activity comparable to subcutaneously administered regular human insulin. In patients with type 1 diabetes, EXUBERA should be used in regimens that include a longer-acting insulin. In patients with type 2 diabetes, EXUBERA can be used as monotherapy or in combination with oral agents or longer-acting insulins."

Because of this proposed labeling regarding indications, the clinical reviewer considered four potential indications:

- control of hyperglycemia in Type 1 diabetics (inhaled insulin in combination with a longer-acting insulin (Section 6.1)

- control of hyperglycemia in Type 2 diabetes (inhaled insulin monotherapy) (Section 6.2)
- control of hyperglycemia in Type 2 diabetes (inhaled insulin in combination with oral agents) (Section 6.4)
- control of hyperglycemia in Type 2 diabetes (inhaled insulin in combination with longer-acting insulins) (Section 6.3)

Although the applicant does not seek an indication for the use of Exubera® in children, the clinical reviewer anticipates significant interest in the use of inhaled insulin in children, and therefore efficacy data regarding pediatric use were also considered (Section 6.5).

In general, the major Phase 3 trials met the definition of "adequate and well-controlled" studies contained in 21 CFR 314.126. One concern regarding trial design was the method of treatment assignment (6.1.3.2). Patients were assigned to their treatment groups by block allocation within center rather than by true randomization, and it may have been possible for an investigator to predict the treatment group assignment of the next patient in a block. The investigator could then have chosen a "better" patient if the investigator could predict that the next patient would go to the inhaled insulin group, or a "worse" patient to go to the SQ group. However, statistical analyses did not reveal evidence of bias related to this treatment allocation method. All studies were open label, and none used inhaler or injection placebos. Historically, clinical trials of insulin have generally not been blinded trials, due to safety, logistical, and ethical concerns.

For the most part, exclusion criteria used in Phase 2 and Phase 3 trials were unlikely to limit the general applicability of trial results. However, the following exclusion criteria could have excluded significant numbers of diabetics who might be encountered in clinical practice (Section 7.2.1.2):

- BMI >35 kg/m^2 for Type 2 diabetics
- HbA1c >12%
- Renal impairment
- Requirement of >150 units per day of subcutaneous insulin
- Signs of autonomic neuropathy, such as gastroparesis or orthostatic hypotension
- Tobacco smoking within 6 months of study or during study
- Two or more serious hypoglycemic episodes within the year prior to study
- Hospitalization or emergency room visit within the six months prior to study for poor diabetes control

Information regarding the efficacy and safety of large doses of inhaled insulin, such as that required for very obese patients, and those who have already demonstrated a high subcutaneous insulin requirement, is lacking. Significant renal impairment and autonomic neuropathy are common complications of diabetes. Although the applicant proposes in its label to exclude smokers from use of inhaled insulin, it is likely that smokers will use the drug, either because the smoking exclusion is not noted by prescribing clinicians, or because patients do not share their smoking history with their physicians.

The proposed indication for combined use of inhaled insulin and a longer-acting insulin for the treatment of Type 1 diabetes was addressed in Studies 106 and 107 (Section 6.1). Of these, 107 was most relevant, because inhaled insulin and the comparator insulin were both administered in an "intensive" fashion, similar to that used in the landmark Diabetes Control and Complications Trial (DCCT), which demonstrated that "tight" control of HbA1c resulted in a lowered risk of diabetic complications in Type 1 patients. The standard of care for Type 1 diabetes now includes a HbA1c <7.5%, with <6.5% recommended by the American Association of Clinical Endocrinologists. In Study 107, inhaled insulin was noninferior to subcutaneous insulin with regard to the primary endpoint, change from baseline in HbA1c (Section 6.1.4.2). Mean HbA1c went from 8.0% to 7.7% at 24 weeks in the inhaled insulin group, and from 8.0% to 7.8% in the SQ group. This mean value for both groups is higher than that achieved in the intensive control group in the DCCT. Although 64% of inhaled insulin group patients achieved a HbA1c <8% by 24 weeks, only 23% achieved a HbA1c <7% (Section 6.1.4.3.1). Inhaled insulin was associated with significantly lower fasting plasma glucose at end-of-study than was subcutaneous insulin, but more patients on inhaled insulin had undesirably low fasting plasma glucoses, also (Section 6.1.4.3.2). This observation was not due to differences in evening longacting insulin doses. Rates of severe hypoglycemia were also higher in the inhaled insulin group than in the SQ group by the applicant's analysis (Section 7.1.3.3.1.1). However, the FDA Biostatistics review calls into question the statistical model used by Pfizer for comparison of hypoglycemic event rates. Reanalysis by the FDA Biostatistics reviewer is ongoing as of 4 Aug 05, but it appears that a more appropriate model may show that severe hypoglycemia event rates did not actually differ between groups. Postprandial glucose excursion was moderately numerically and statistically significantly greater in inhaled insulin group patients than in subcutaneous group patients, which is undesirable due to an epidemiologic association of postprandial glucose levels with cardiovascular risk (Section 6.1.4.3.3). Noninferiority of the inhaled insulin regimen to the subcutaneous regimen in this trial does not necessarily indicate noninferiority of this inhaled regimen to the intensive subcutaneous regimen used in the DCCT. By the best-validated surrogate endpoint available (HbA1c), intensive control of Type 1 diabetes appears possible for some patients with inhaled insulin. However, it is not clear from this trial whether the average Type 1 diabetic taking inhaled insulin can attain glycemic control commensurate with the clearly established standard of care, and the risk of severe hypoglycemia appears higher (by the applicant's analysis) than that seen with an intensive subcutaneous insulin control. Special attention may be needed to ensure control of postprandial glucose excursion, and to avoid fasting and severe hypoglycemia.

Two major trials in Type 2 diabetics included an inhaled insulin monotherapy arm compared to oral agent(s) (Section 6.2). Study 109 enrolled patients who were poorly controlled on combination oral agent therapy, and randomized patients to one of three arms: premeal inhaled insulin monotherapy, premeal inhaled insulin plus the patient's baseline oral agents, or continued combination oral agents. Study 110 compared premeal inhaled insulin monotherapy to rosiglitazone treatment. In Study 109, inhaled insulin monotherapy was superior to continued oral agent therapy for change in HbA1c at Week 12, for this population that was failing oral agent therapy at baseline (Section 6.2.4.2.1). Inhaled insulin monotherapy was superior to continued oral agent therapy for achievement of HbA1c <8% and <7%, for this population that was failing oral agent therapy at baseline (Section 6.2.4.2.2.1). Inhaled insulin monotherapy was

superior to continued oral agent therapy in reduction of fasting plasma glucose and postprandial glucose excursion in this population that was failing oral agent therapy (Section 6.2.4.2.2.2). In Study 110, inhaled insulin monotherapy was superior to rosiglitazone for the primary endpoint, percentage of patients achieving a HbA1c <8% (Section 6.2.4.3.1). A higher percentage of patients in the inhaled insulin group also achieved a HbA1c <7%. Inhaled insulin treatment resulted in a greater decline in HbA1c than that seen with rosiglitazone (Section 6.2.4.3.2.1). The difference between groups was not significant for change from baseline in FPG and postprandial glucose excursion (Section 6.2.4.3.2.2). From Study 109, it appears that inhaled insulin monotherapy is effective in achieving better glucose control (by HbA1c) for Type 2 patients who are failing combination (dual) oral agent therapy. From Study 110, inhaled insulin monotherapy appears superior to rosiglitazone in achieving HbA1c goals in Type 2 patients not previously exposed to injected insulin.

Study 108 was the major completed trial utilizing inhaled insulin in combination with a longer-acting insulin for Type 2 diabetics, and review focused on this study (Section 6.3). Study 108 was a 6 month, block-allocated, open-label, parallel group study done in Type 2 patients who had been on a stable regimen of SQ insulin for at least 2 months prior to study entry, and who had entry HbA1cs between 8 and 11%. Patients were assigned to receive either TID premeal inhaled insulin plus bedtime Ultralente® (UL), or BID mixed SQ NPH and regular insulin. The objective was to determine if inhaled insulin administered in this regimen was at least as effective (in control of HbA1c) as BID mixed SQ insulin. Treatment assignment was by block allocation within center as previously described for other studies. The clinical reviewer had some concern regarding the lower intensity of management in the SQ group (two insulin doses per day) compared to the inhaled insulin group (four insulin doses per day). The increased attention to self-care required for a four time per day intervention might in itself result in a greater decrease in HbA1c than one could achieve with a twice daily intervention. However, a twice daily injected insulin regimen is commonly used in Type 2 diabetes, and thus permits comparison to "usual care". Likely clinical scenarios of use for inhaled insulin in Type 2 diabetics would be either one in which the patient is on a mixed BID regimen and wishes to take fewer injections per day, or one in which the clinician or patient desires tighter control, but wishes to spare the patient a four shot per day regimen. In these cases, substitution of a TID premeal inhaled insulin plus a q day basal SQ injection would be likely. It will be important in this scenario to know if one would be putting the patient at risk of more hypoglycemic episodes in general, or of more serious hypoglycemic episodes. This trial design permits exploration both of the efficacy of this premeal inhaled + q day basal SQ regimen, and of the safety of the regimen with regard to the possibility of increased hypoglycemia. Furthermore, it appears that the likely efficacy of the inhaled insulin portion of this regimen is not in question, because in Study 109 (Section 6.2.4), inhaled insulin monotherapy was effective in improving glycemic control in Type 2 diabetics who were failing dual oral agent therapy. For change from baseline in HbA1c, the premeal inhaled insulin plus hs UL regimen used in Study 108 was noninferior to the BID mixed SQ regimen (Section 6.3.4.2). A slightly higher percentage of patients in the intensively-administered inhaled insulin group achieved HbA1cs of <8% and <7% than did patients in the BID SQ group (Section 6.3.4.3.1). Fasting plasma glucose declined more in inhaled insulin group patients; there was no significant difference in the change in postprandial glucose increment (Section 6.3.4.3.2). In Study 108, a regimen of TID premeal inhaled insulin plus

bedtime UL was noninferior to a regimen of BID SQ mixed regular and NPH insulin, for the control of HbA1c in Type 2 diabetics. By the applicant's analysis, rates of hypoglycemia did not differ between treatment groups; reanalysis by FDA Biostatistics is ongoing. The applicant provided an interim analysis of an ongoing study, Study 1029, which, when complete, will provide a comparison of TID premeal inhaled insulin to TID premeal SQ insulin, when both are administered with a longer-acting subcutaneous insulin (Section 6.3.6). In this study, patients in the inhaled insulin group are receiving TID premeal inhaled insulin plus hs intermediate to long-acting insulin (UL, NPH or glargine), and patients in the SQ group are receiving TID premeal insulin (regular, aspart or lispro) and hs intermediate to long-acting insulin (UL, NPH or glargine). A one-year interim analysis of this study indicates noninferiority of the inhaled regimen(s) to the SQ regimen(s), with changes from baseline in HbA1c of -0.53 (SE 0.05) for the inhaled insulin group and -0.60 (SE 0.05) for the SQ group.

Regarding the proposed indication for combined use of inhaled insulin and oral agents for control of hyperglycemia in Type 2 diabetes, the applicant submitted the results of Studies 109, 1001, and 1002 (Section 6.4). Study 109, which was also used to support inhaled insulin monotherapy, included an arm with TID premeal inhaled insulin plus continued combination oral hypoglycemic agents (insulin secretagogue, plus glitazone or metformin). Study 1001 combined inhaled insulin with a sulfonylurea, and Study 1002 combined inhaled insulin with metformin. Study 1001 included patients who were already poorly controlled on sulfonylurea therapy and had HbA1cs between 8 and 12%. HbA1c strata included 8-9.5%, and >9.5-12. Patients were assigned to one of two groups: TID premeal inhaled insulin + continued SU, or metformin (1 gm BID) + continued SU. Study 1002 included patients who were already poorly controlled on metformin (1 gm BID) and had HbA1cs between 8 and 12%. HbA1c strata included 8-9.5%, and >9.5-12. Patients were assigned to one of two groups: TID premeal inhaled insulin + continued metformin, or glibenclamide (maximum dose 5 mg BID) + continued metformin. For Study 1001, for the primary efficacy endpoint of change from baseline in HbA1c, the 6-month data did not support superiority of the addition of inhaled insulin over the addition of sulfonylurea to failed metformin therapy (Section 6.4.4.2). For Study 1002, for the primary efficacy endpoint of change from baseline in HbA1c, the 6-month data did not support superiority of the addition of inhaled insulin over the addition of metformin to failed sulfonylurea therapy (Section 6.4.4.2). However, for both studies, the addition of inhaled insulin appeared noninferior to the addition of the comparator oral agent. In Study 109, the addition of inhaled insulin to continued failed combined (dual) oral agent therapy appeared superior to continued failed combined (dual) oral agent therapy alone for change from baseline in HbA1c at 3 months (Section 6.2.4.2.1). For both Studies 1001 and 1002, the addition of inhaled insulin resulted in a greater percentage of patients achieving HbA1cs <8% than did addition of the comparator agent (Section 6.4.4.3.1). Patients with higher HbA1cs at baseline (>9.5-12%) were more likely to achieve a HbA1c <7% with the addition of inhaled insulin than with the addition of the comparator, although the percentage of patients in either treatment group who achieved a HbA1c <7% was small. In Study 109, the addition of inhaled insulin to continued failed combined oral agent therapy appeared superior to continued failed combined oral agent therapy alone for achievement of HbA1cs <8% and <7% (Section 6.2.4.2.2.1). Overall, the addition of inhaled insulin to a failed oral agent appears at least noninferior to the addition of a second oral agent for the control of Type 2 diabetes. Addition of inhaled insulin to failed combined (dual)

oral agent therapy appears superior to continued failed combined oral agent therapy alone. The combination of inhaled insulin and failed combined oral agent therapy resulted in greater favorable changes in measures of glucose control in Type 2 diabetes than did inhaled insulin monotherapy, which in turn was also superior to continued failed combined oral agent therapy alone.

Regarding Type 1 diabetic pediatric use of inhaled insulin, Studies 106 and 107 included adolescents ages 12-17 years, and Study 1009 included children ages 6-11 years (Section 6.5). No children ages 5 and under were studied. Studies 106 and 107 were described above regarding use in adult Type 1 diabetics (Section 6.1.3). Study 1009 was a 3-month study conducted in Type 1 diabetic children ages 6-11 years (Section 6.5.3). A total of 120 children (61 in inhaled insulin group) were treated with either an inhaled insulin regimen (TID premeal inhaled insulin + hs or BID UL or NPH) or a SQ regimen (BID lispro or regular + q day or BID UL or NPH). There was little difference between treatment groups for change from baseline in HbA1c in Studies 106, 107 and 1009 (Section 6.5.4.1). Neither treatment group attained "tight" control of mean HbA1c in any of these studies, with mean HbA1c remaining above 8% in all treatment groups. Inhaled insulin patients had little change from baseline in HbA1c. In Study 1009, a slightly larger percentage of children ages 6-11 achieved HbA1cs <8% and <7% in the inhaled insulin group than did children in the SQ group (Section 6.5.4.2.1). In Study 1009, mean fasting plasma glucoses remained undesirably high in both treatment groups, with no significant difference between groups (Section 6.5.4.2.3). There was no significant difference between groups for change in postprandial glucose excursion, with small declines in both treatment groups. Studies performed in children and adolescents to date do not appear to show that the desirable level of glucose control (i.e. that associated with decreased risk for later diabetic complications) can be predictably achieved with inhaled insulin. Should Exubera® be approved for use in adults, further study in children appears warranted.

In the overall Phase 3 program, for both Type 1 and Type 2 diabetics, the mean dose of long-acting insulin for inhaled insulin group patients was somewhat lower than that for subcutaneous insulin patients (Section 7.2.1.3). The mean dose of inhaled insulin gradually increased over time, while the dose of subcutaneous short-acting insulin increased from baseline to Month 3, and then remained stable until Month 12. It is difficult to attach particular significance to either of these observations. The mean lower dose of long-acting insulin for inhaled insulin patients implies that, on average, glycemic control was not disproportionately "carried" by the long-acting component of inhaled insulin patients' regimens. The gradual increase in inhaled insulin dose without a corresponding increase in short-acting SQ dose could indicate developing resistance to the action of inhaled insulin, or neutralization of insulin action by insulin antibodies; or it could merely represent increasing familiarity and comfort with upward titration of a novel agent. In major diabetes trials, such as UKPDS and DCCT, insulin dose tended to increase gradually over time; however, it is not clear why this occurred in the inhaled insulin group here and not in the SQ group.

9.1.2 Safety Conclusions

A total of 22 deaths occurred among 3,603 subjects (0.6%) exposed to inhaled insulin in the clinical development program, as of the safety cut-off date of 1 Sep 04 (Section 7.1.1). Of these, 21 patients were participants in the clinical development program and one was a neonate born of a mother exposed to inhaled insulin. Ten deaths, including that of the neonate, occurred during controlled Phase 2/3 trials, which included 1,975 adult patients (0.5%). Twelve deaths occurred during extension studies, which included 1,449 patients (0.8%). Five patients who received comparator drugs died, out of 1,938 comparator patients (0.3%). When taking into account the longer duration of exposure for inhaled insulin groups, there is little difference in mortality rates between inhaled insulin and comparator treatments.

Of the adult patients who died during the clinical development program, 15/21 appear to have died of cardiac causes. Most diabetics die of cardiovascular disease, and the percentage of deaths which were due to cardiovascular disease during the study of this product is consistent with the usual incidence of cardiovascular death among diabetics. Those patients who died of acute causes do not appear to have had an unusually high incidence of severe hypoglycemic events (those requiring the assistance of another person, or events with a blood sugar <36 mg/dL). However, four of these patients had histories of a large number of nonserious hypoglycemic events, and one death occurred shortly after what appears to have been a hypoglycemic episode. Overall, the deaths which occurred in inhaled insulin group patients do not seem to have a stronger association with hypoglycemia than expected in diabetics treated with subcutaneous insulin. A total of 7/21 of these deaths occurred in Type 1 diabetics who were taking inhaled insulin. The rate of death among Type 1 inhaled insulin patients does not exceed that found in the intensive treatment groups of large randomized trials in Type 1 diabetics. No clear difference was demonstrated between inhaled insulin and comparator patients for incidence or cause of death.

In controlled Phase 2 and Phase 3 studies in adult Type 1 patients, serious adverse events occurred at a slightly higher frequency in SQ group patients than in inhaled insulin group patients (Section 7.1.2.1.1). The most common serious adverse events among Type 1 patients were hypoglycemia and loss of consciousness. In the controlled Phase 2/3 population, these events occurred with slightly greater frequency in SQ patients than in inhaled insulin patients. In Type 1 adult patients, no pattern emerged of a single type of serious nonpulmonary adverse event, or grouping of serious nonpulmonary adverse events, that occurred with significantly greater frequency among inhaled insulin group patients than among SQ patients. Pulmonary serious adverse events will be discussed separately in Dr. Seymour's review. Event terms potentially related to hypoglycemia did not occur more frequently in Type 1 adult patients receiving inhaled insulin, and appear to have occurred less frequently numerically among inhaled insulin patients than among patients receiving SQ insulin.

In controlled Phase 2 and Phase 3 studies in Type 2 patients, serious adverse events occurred with approximately equal frequency among inhaled insulin patients and comparator patients (Section 7.1.2.1.2). Myocardial infarction, chest pain, angina and hypoglycemia were the most common SAE terms among Type 2 patients. Inhaled insulin group patients did not have a significantly higher frequency of serious nonpulmonary adverse event term groupings of interest, such as terms related to coronary artery disease, hypoglycemia, loss of consciousness, seizure,

accidents, injuries, neoplastic events, or immune system disorders. Hypoglycemia adverse event terms occurred numerically more frequently among SQ patients than among inhaled insulin patients or OA patients. Pulmonary adverse event term groupings will be addressed in Dr. Seymour's pulmonary review.

Hypoglycemia reported as a serious adverse event occurred somewhat more frequently among children taking inhaled insulin than among children taking SQ insulin (Section 7.1.2.1.3). Otherwise, no single type of serious adverse event or grouping of adverse events occurred more frequently among pediatric patients taking inhaled insulin than among pediatric patients taking SQ only. Almost all serious adverse events among pediatric patients were related to hypoglycemia. Severe hypoglycemia was reported as a serious adverse event term more frequently among pediatric patients than among either adult Type 1or Type 2 patients.

When evaluating serious hypoglycemic adverse events, the clinical reviewer also considered whether the nature of serious hypoglycemic adverse events differed between inhaled insulin and comparator patients (Section 7.1.2.3). The clinical reviewer examined all adverse event narratives provided by the applicant, and identified those events which had serious accompanying events, e.g. loss of consciousness, syncope, accidents and injuries. Adult inhaled insulin group patients do not appear to have had a higher incidence of potentially dangerous accompanying events to serious hypoglycemic episodes than did comparator patients.

For further evaluation of serious adverse events, the clinical reviewer compared the event terms used by the applicant in its serious adverse event listings to the terms used by the investigators (Section 7.1.2.3). This was done in order to ascertain whether the nature of serious adverse events could have been downplayed in the inhaled insulin groups, or embellished in the comparator groups. Upon review of all serious hypoglycemic event narratives, the clinical reviewer noted some cases in which the event was reported only as hypoglycemia, and an accompanying accident or injury was not mentioned in the listing. Although the serious adverse event listings for hypoglycemic events sometimes did not include mention of an accompanying accident or injury, this reconciliation difference did not occur more frequently among inhaled insulin patients than among comparator patients. Terms used for other types of serious adverse events in the applicant's serious adverse event listings almost always reconciled closely with those found in provided event narratives.

Because diabetic ketoacidosis is the leading cause of mortality among pediatric Type 1 diabetics, it was an event of significant interest (Section 7.1.2.3). No deaths from diabetic ketoacidosis occurred in children in this development program, and no cases of cerebral edema accompanying DKA were reported. Pediatric serious adverse events of diabetic ketoacidosis did not occur more frequently among inhaled insulin patients than among SQ patients in controlled Phase 2/3 trials (one case among inhaled insulin patients, two cases among SQ patients). In the extension study 111, a total of 21 serious adverse events of ketoacidosis occurred among 17 patients. This study had a large total duration of exposure for pediatric patients, with a total of 5,801 subject-months of exposure. Comparative incidence rates for DKA were 0.04 cases of diabetic ketoacidosis per child-year for inhaled insulin patients in all Phase 2/3 trials and 0.04 cases of DKA per child-

year for SQ patients in controlled Phase 2/3 trials. In the medical literature, the reported incidence of DKA (after initial diagnosis) ranges from 1-10% per year (Dunger 2003).

When considering all adverse events (serious and nonserious), in controlled Phase 2/3 studies in Type 1 diabetics, the overall incidence of adverse events was similar between inhaled insulin patients and SQ patients, with 99.4% and 98.7% of patients, respectively, experiencing some type of adverse event (Sections 7.1.5.3 and 7.1.5.4). In controlled Phase 2/3 studies in Type 2 patients, adverse events occurred with nearly equal frequency between inhaled insulin patients [93.7% with event(s)] and SQ patients [96.7% with event(s)]. Among Type 2 patients treated with oral agents, 81.7% experienced an adverse event. This lower rate among oral-agent treated patients is due to a lower rate of hypoglycemia among these patients than among inhaled insulin or SQ patients (Section 7.1.5.4).

Hypoglycemia was the most common adverse event among Type 1 patients, and occurred with equal frequency in inhaled insulin and SQ group patients (Section 7.1.5.4). Cough was a common adverse event, and occurred with significantly greater frequency among inhaled insulin patients (196/698, 28.1%) than among SQ patients (59/705, 8.4%). Other respiratory adverse events (dyspnea, respiratory disorder) also occurred with greater frequency among inhaled insulin patients. Nasopharyngeal adverse events (epistaxis, pharyngitis, rhinitis, sinusitis) occurred at a higher frequency in inhaled insulin groups (310/698, 44.4%) than in SQ groups (220/705, 31.2%). Adverse event terms related to accidents occurred with equal frequency between groups. The event term "allergic reaction" occurred with slightly greater numeric frequency in inhaled insulin patients (31/698, 4.4%) than among SQ patients (23/705, 3.3%).

Among Type 2 patients, hypoglycemia was the most common adverse event term, and occurred most commonly in SQ patients (360/488, 73.8%) (Section 7.1.5.4). Inhaled insulin patients had a lower rate of hypoglycemic events than SQ patients, but had a higher rate than OA patients [inh ins = 794/1277 (62.2%), OA = 185/644 (28.7%)]. Cough was also very common, and occurred with significantly higher frequency among inhaled insulin patients than among comparator patients (inh ins 21.0%, SQ 7.4%, OA 3.7%). Accident and injury terms occurred numerically more frequently among SQ patients than among other groups. Several respiratory events (e.g. asthma, bronchitis, dyspnea) had a somewhat higher frequency among inhaled insulin patients than among comparator patients; please see Dr. Seymour's pulmonary review for discussion. Headache and paresthesia occurred at a slightly higher numeric rate in inhaled insulin groups than in comparator groups.

Hypoglycemic event rates did not differ between pediatric inhaled insulin and SQ patients (Section 7.1.5.4). Among pediatric patients, the adverse event term seen with the greatest excess frequency for inhaled over SQ was cough. Nausea, headache and dizziness also occurred numerically more frequently in inhaled insulin patients than in SQ patients. When combining ear terms, adverse events related to the ear occurred more frequently in children in inhaled insulin groups than in children in SQ groups. The terms ear pain, ear disorder and otitis media had a combined event rate of 18/153 (11.8%) in the inhaled insulin patients vs 7/148 (4.7%) in SQ patients. This difference could be due to chance; however, the Eustachian tube in children provides an anatomically more direct route to the middle ear than does the Eustachian tube of the

adult, and the possibility of entry of inhalation powder into the Eustachian tube of children is a consideration.

Common adverse events which seem likely to be related to inhaled insulin use include cough; nasopharyngeal adverse events such as pharyngitis, rhinitis and sinusitis; and certain respiratory adverse events such as dyspnea (Sections 7.1.5.4 and 7.1.5.5). Adverse events related to the ear seem to be related to inhaled insulin in children (Sections 7.1.5.4 and 7.1.5.5).

There is no clear relationship between age and incidence of rhinitis or sinusitis in patients exposed to inhaled insulin, and dose-dependency was not demonstrated. Inhaled insulin patients who developed rhinitis did so sooner than SQ patients who developed rhinitis (Section 7.1.5.6).

Regarding serious but rare adverse events, the events "eye hemorrhage" and "retinal hemorrhage" occurred more frequently per unit of patient-time over all Phase 2/3 trials than these events occurred per unit of patient time in comparator groups in the controlled Phase 2/3 trials (Section 7.1.6). Events termed "allergic reaction" occurred at a somewhat higher frequency per unit of patient-time among inhaled insulin patients in the population of all Phase 2/3 trials than among comparator patients in the controlled Phase 2/3 trials. Concern exists for the development of undesirable immune responses to inhaled insulin. Malignant neoplasms did not occur with greater frequency in inhaled insulin patients per unit of patient-time than in comparator patients.

Hypoglycemia reported as a serious adverse event was discussed above with other serious adverse events (Sections 7.1.2.2 and 7.1.2.3). Hypoglycemia was also evaluated in two other ways (Section 7.1.3.3.1).

In individual studies, the applicant defined severe hypoglycemic events as those in which all three of the following criteria were met:

- the patient was unable to self-treat
- the patient exhibited at least one of the following- memory loss, confusion, uncontrollable behavior, irrational behavior, unusual difficulty in awakening, suspected seizure, loss of consciousness
- measured blood glucose was ≤ 49 mg/dL; or if no blood glucose was measured, clinical manifestations were reversed by oral carbohydrates, subcutaneous glucagon, or intravenous glucose.

For the overall safety review, severe hypoglycemia was defined as an event in which the subject had a measured blood glucose of ≤ 36 mg/dL and/or required assistance. The specified blood glucose was requested by a previous FDA clinical reviewer.

For adult Type 1 patients overall, inhaled insulin was not associated with a higher rate of severe hypoglycemia (BG ≤ 36 mg/dL or required assistance) than was SQ insulin (Section 7.1.3.3.1.1). However, in Study 107, the "intensive control" study in Type 1 diabetics, severe hypoglycemic events (by the applicant's study definition) did appear to occur more frequently in the inhaled insulin group than in the SQ only group (Section 7.1.3.3.1.1), by the applicant's analysis. This

could be an important finding, because intensive control is now the standard of care for Type 1 diabetics, and severe hypoglycemia tends to be the limiting factor in achieving tight control. However, it should be noted that FDA Biostatistics review calls into question the statistical model used by Pfizer for comparison of hypoglycemic event rates. Reanalysis by the FDA Biostatistics reviewer is ongoing as of 4 Aug 05, but it appears that a more appropriate model may show that severe hypoglycemia event rates did not actually differ between treatment groups.

Among Type 1 diabetics overall, in both the inhaled insulin and SQ groups, overall hypoglycemic (severe and nonsevere) event rates declined over time, with similar rates of decline between groups (Section 7.1.3.3.1.1). This could indicate an initial period of adjustment to the study regimen, with declining incidence of severe hypoglycemic events as the study progressed, or a decline in reporting of clinical events. Although there was an apparent decline over time in controlled Phase 2/3 studies, severe hypoglycemic adverse events continued to occur in extension studies; the occurrence of severe hypoglycemic adverse events cannot be entirely attributed to an initial learning period for inhaled insulin (Appendix 10.5).

Among Type 1 diabetics, inhaled insulin group patients tended to have higher hypoglycemic event rates in the early morning than did SQ group patients, while the converse was true for midday (Section 7.1.3.3.1.1). This was observed for the overall pattern in Phase 2 and Phase 3 trials, and held true across most studies. The reason for this consistent pattern of prebreakfast hypoglycemia in inhaled insulin group patients is unclear. One would expect prebreakfast hypoglycemia to be related to evening dosing of longacting insulin, rather than to the patient's short-acting insulin. However, in Study 107, the intensive control study in Type 1 diabetics, mean dose of longacting insulin was actually somewhat lower for inhaled insulin group patients, both for the evening dose and for the total daily dose (Section 6.1.4.3.2). Study 1026 was the only study in which 0200 blood sugars were routinely measured (Section 6.1.4.3.2). In this study, hypoglycemia was more common at 0200 for inhaled insulin group patients than for SQ patients. For the overall population of Type 1 diabetics in all Phase 2/3 studies, the majority of hypoglycemic episodes reported as serious adverse events among inhaled insulin patients occurred in the early morning hours (for those patients for whom serious adverse event narratives were provided) . Inhaled insulin appears to be more likely (by the applicant's analysis) than SQ insulin to cause severe hypoglycemia in intensive management of Type 1 diabetes; for unknown reasons, these severe hypoglycemic events among intensively managed inhaled insulin patients appear to occur more often in the early morning hours (Appendix 10.5).

Overall, severe hypoglycemic events were less common among patients with Type 2 diabetes compared to patients with Type 1 diabetes (Section 7.1.3.3.1.2). Inhaled insulin group patients were not more likely to experience severe hypoglycemic events than SQ group patients, in studies of Type 2 patients who were using insulin at baseline. However, inhaled insulin group patients were more likely to experience severe hypoglycemia than were patients in oral agent comparator groups in studies of patients who were not insulin-using at baseline. Control of glycemia was in general better with inhaled insulin than with oral agents, and thus a higher rate of hypoglycemia would be expected. In Studies 104, 109 and 110, all severe hypoglycemic events occurred in inhaled insulin group patients. The FDA Biostatistics reviewer is reanalyzing these hypoglycemic data in the same manner as the reanalyses for Type 1 diabetic patients.

In studies of Type 2 diabetics where SQ was used as a comparator, rates of hypoglycemia declined over time for both SQ and inhaled insulin patients (Section 7.1.3.3.1.2). In studies of Type 2 diabetics where oral agents were used as a comparator, event rates were too low to distinguish a time trend. The applicant provided data regarding time of day of hypoglycemic events for Type 2 patients, but the number of events was too low to discern a trend for any particular time of day.

In Studies 106 and 1009, children and adolescents who were treated with inhaled insulin were somewhat less likely to experience protocol-defined hypoglycemia (severe or nonsevere) than patients who were taking SQ insulin (Section 7.1.3.3.1.3). In Study 107, there was no demonstrated difference between groups. Protocol-defined severe hypoglycemic events did not occur more frequently among pediatric inhaled insulin patients in Studies 106 and 1009. In Study 107, there were 16 events of severe hypoglycemia in the inhaled insulin group, and 10 events in the SQ group. Although the risk ratio was 1.62 for occurrence of severe hypoglycemia for inhaled insulin-treated adolescents vs SQ-treated adolescents, the limits of the confidence interval fell on either side of 1, and therefore the difference between groups was not statistically significant. Overall, protocol-defined hypoglycemia, and protocol-defined severe hypoglycemia, did not appear to occur statistically significantly more frequently in pediatric patients treated with inhaled insulin compared to those treated with SQ alone. Biostatistics reanalysis of hypoglycemic event data is ongoing.

Dose dependency of adverse events was explored (Sections 7.4.2.1 and 7.1.5.6). Among Type 1 diabetics, increased sputum production may be dose-related. When one examines the overall incidence of accidents and fractures, these events occurred at a higher numerical rate in patients on higher doses. This is of concern, because of the variability in delivered dose of the device (Section 3.1), which could increase the risk for hypoglycemia and attendant events of accident or injury. The problems with dose proportionality and dose equivalence could also lead to increased risk for hypoglycemia (Section 5.1). For serious adverse events of accident and injury, the applicant specifically examined each event to look for a relationship to hypoglycemia; no difference was noted between treatment groups for incidence of hypoglycemia-related serious accidents and injuries.

Among Type 2 diabetics, the incidence of dyspnea appeared to be dose-related (Section 7.4.2.1). Several respiratory events occurred with lower frequency in patients who were taking <10 mg/day of inhaled insulin than in those taking ≥ 10 mg/day, but with roughly equal frequency between patients taking 10-20 mg/day and those taking >20 mg/day. These events included total respiratory events, bronchitis, respiratory tract infection, and rhinitis. The overall incidence of cardiovascular events appeared to be dose-related, although no one type of event predominated. Accidental injury and fracture also appeared to be dose-related, with the same concerns as discussed in the above paragraph for this finding in Type 1 patients. Retinal disorders appear to be dose-related. The overall incidence of malignant neoplasms does not appear to be dose-related, nor does the incidence of any single malignancy. While the possible dose-relatedness of some of these events is concerning, these findings must be interpreted with caution. As Type 2 diabetes progresses, beta cell failure occurs with progressive loss of endogenous insulin secretion

and increasing requirement for drug therapy, and eventually with increasing insulin requirement. A higher insulin requirement may be a reflection of duration of disease, which is in turn associated with aging; either duration of disease or aging could be associated with an increased incidence of many adverse events.

Time dependency of adverse events was also explored (Section 7.4.2.2). Among Type 1 patients, for respiratory events in general, and for some specific respiratory events (cough, respiratory tract infection, rhinitis, sputum increased, epistaxis), the time interval in which these adverse events were more likely to be reported (per patient) was during the first 6 months of inhaled insulin treatment. Decreased reporting of these events in subsequent treatment time intervals could either be due to a true decrease in the occurrence of the event, to dropout due to the event, or to nonreporting by patients who felt they had already brought the event to the attention of investigators, and therefore did not report it again. For Type 1 patients, accidental injury, motor vehicle accidents, and accidental fractures were more likely to be reported (per patient) during the time interval beyond 24 months. This could be due to a true increase in the incidence of the events, or to longer per-patient exposure during this time period. Among Type 1 patients, hyperglycemia and hypoglycemia were more likely to be reported as adverse events (per patient) in the time interval of 0-6 months of inhaled insulin treatment. This may be due to the learning process involved in instituting a novel treatment. As with respiratory adverse events, decreased reporting of these metabolic events in subsequent treatment time intervals could either be due to a true decrease in the occurrence of the event, to dropout due to the event, or to nonreporting by patients who felt they had already brought the event to the attention of investigators, and therefore did not report it again. For Type 1 patients, retinal disorders were more likely to be reported (per patient) during the time interval beyond 24 months. This could be due to a true increase in the incidence of the events, or to longer per-patient exposure during this time period.

Among Type 2 patients, for respiratory events in general, and for some specific respiratory events (cough, respiratory tract infection, epistaxis), the time interval in which these adverse events were more likely to be reported (per patient) was during the first 6 months of inhaled insulin treatment (Section 7.4.2.2). Accidental injuries and fractures were more likely to be reported (per patient) during the time interval beyond 24 months. Hypoglycemia was more likely to be reported as an adverse event (per patient) in the time interval of 0-6 months of inhaled insulin treatment. This may be due to the learning process involved in instituting a novel treatment. No clear temporal pattern emerged among Type 2 patients for malignant neoplasms in general or for any particular neoplasm. For Type 2 patients, retinal disorders were more likely to be reported (per patient) during the time interval beyond 24 months.

Demographic interactions for adverse events were also explored (Section 7.4.2.3). A summary of the observations for demographic differences for adverse events includes:

- Numbers of non-Caucasian patients were too small to permit meaningful comparisons between treatment groups.
- For Type 1 patients, the event "sputum increased" had a higher incidence in older patients and in males for inhaled insulin patients, than it had in SQ patients.

- For Type 1 patients in the SQ group, overall respiratory events occurred with decreasing frequency by age group, but in inhaled insulin patients, overall respiratory events occurred with approximately equal frequency between age groups. For patients age 18 and older, overall respiratory events occurred more frequently among inhaled insulin group patients than among SQ patients.
- For Type 1 diabetic children, otitis media occurred more frequently in inhaled insulin group children than in SQ group children. Otitis media occurred with low and approximately equal frequency in adult Type 1 patients in both treatment groups.
- For Type 1 patients, the events "allergic reaction" and "diarrhea" occurred with higher frequency among males than among females in the inhaled insulin group. This gender difference was not apparent in comparator groups.
- For Type 2 patients, the event "dry mouth" appeared to decrease in incidence with age in inhaled and oral agent groups, but not in the SQ group.
- For Type 2 patients, for all treatment groups, women were more likely to experience cough than men; for both genders, cough occurred much more frequently in inhaled insulin group patients than in comparator patients.
- For Type 2 patients, the incidence of bronchitis increased by age group for inhaled insulin patients, but not for comparator patients.
- For Type 2 patients, accidental injury, hypoglycemia, and respiratory tract infection occurred more frequently in men than in women in the inhaled insulin group. This gender difference was not observed in the comparator groups.
- For Type 2 patients, paresthesia occurred more frequently in women than in men in the inhaled insulin group. This gender difference was not observed in the comparator groups.

Among these observations, those most likely to have clinical significance include:
- Otitis media in children appears related to inhaled insulin treatment.
- The incidence of bronchitis appears to increase by age group for inhaled insulin patients, but not for comparator patients.
- For Type 2 patients, accidental injury and hypoglycemia appear to occur more frequently in men than in women taking inhaled insulin. This gender difference was not observed in the comparator groups.

Across the development program, greater increases occurred in insulin antibody levels for patients taking inhaled insulin than for patients taking either subcutaneous insulin alone or oral agents alone (Section 7.1.3.3.2). This observation led to concerns about potential clinical consequences of this antibody formation. The following points can be synthesized from extensive data regarding insulin antibodies associated with inhaled insulin use, and the potential clinical consequences of these antibodies:
- Seroconversion rates were higher among inhaled insulin patients than among comparator patients (Section 7.1.3.3.2.1). In studies in which a quantitative insulin antibody assay was used, 75% of all inhaled insulin patients who had undetectable insulin antibodies at baseline had measurable insulin antibodies at end of study or last measurement, while only 10% of comparator patients seroconverted. Seroconversion rates for inhaled insulin patients were

higher among Type 1 patients than among Type 2 patients, and were higher among children than among adults.

- For both Type 1 and Type 2 patients, inhaled insulin was associated with higher end-of-study insulin antibody levels, and with greater change from baseline, than was SQ insulin (Section 7.1.3.3.2.2).
- Among Type 1 inhaled insulin patients, pediatric patients had higher end-of-study insulin antibody levels and greater changes from baseline than did patients ≥ age 18 years (Section 7.1.3.3.2.2). Among Type 1 inhaled insulin patients, female patients had higher end-of-study insulin antibody levels and greater changes from baseline than did male patients.
- Among Type 2 patients, patients who had been using injected insulin prior to study enrollment had higher insulin antibody levels at end of study, and greater changes from baseline, than did patients who had not been using injected insulin prior to study (Section 7.1.3.3.2.2). Among Type 2 patients using inhaled insulin, insulin antibody levels appeared to correlate with age.
- Insulin antibodies were predominantly IgG for both inhaled insulin patients and comparator patients (Section 7.1.3.3.2.3). Binding profile was consistent with low affinity, high binding capacity antibodies.
- In general, adverse events of an allergic nature tended to occur with similar frequency between inhaled insulin and SQ group patients (Section 7.1.3.3.2.4). For Type 1 patients, the event terms "allergic reaction" and "rhinitis" occurred somewhat more frequently among inhaled insulin patients than among SQ patients (Sections 7.1.3.3.2.4.1 and 7.1.3.3.2.4.2).
- There were no apparent associations between insulin antibody levels and incidence of hypoglycemic events (Section 7.1.3.3.2.4.2). In controlled Phase 2/3 trials, patients who had severe specifically-defined hypoglycemic events did not tend to have higher antibody levels than patients who did not have severe hypoglycemic events.
- When examining those patients who had the highest insulin antibody titres (>2,000 μU/mL), 33/37 were Type 1 diabetics, and 11 were children (Section 7.1.3.3.2.5). Three of these 33 patients experienced adverse events of a potentially allergic nature (allergic bronchiolitis, dermatitis of face and arms, bilateral eyelid swelling). Among the Type 1 patients with high antibody titres, 9 patients experienced a total of 67 severe hypoglycemic events. These 9 patients represent 27% of the total Type 1 study population; in the overall controlled Phase 2/3 population, 17% of inhaled insulin patients experienced a severe hypoglycemic event. However, when one considers duration of exposure, patients with high antibody titres did not experience severe hypoglycemic events more frequently than did the population of Type 1 patients in all Phase 2/3 trials.
- The applicant made extensive attempts to develop a neutralizing antibody assay, but was unable to do so (Section 7.1.3.3.2.6). Development of neutralizing insulin antibodies might be associated with increasing insulin requirements or worsening indices of glycemic control. However, there was no association between insulin antibody levels and HbA1c, postprandial glucose, fasting glucose or insulin requirement.
- The actual drug substance used did not exhibit inherent immunogenicity in , in which 476 insulin-naïve Type 2 patients were randomized to receive eith) for

one year (Section 7.1.10). Rates of insulin antibody development did not differ between groups.
- Discontinuation of inhaled insulin resulted in a decline in insulin antibody levels, although levels did not return to baseline by 12 weeks of followup (Section 7.1.3.3.2.8).

Overall, it appears that although inhaled insulin patients demonstrate a brisk increase in insulin antibody levels, studies to date do not demonstrate a clinical correlate of this finding.

Observations of note regarding reasons for discontinuation among Type 1 diabetics include (Section 7.1.3.1):
- In controlled trials, discontinuations due to adverse events were more common among inhaled insulin patients than among SQ patients.
- A large number of inhaled insulin patients withdrew consent during uncontrolled portions of Phase 2 and Phase 3 trials

Observations of note regarding reasons for discontinuation among Type 2 diabetics include (Section 7.1.3.1):
- Discontinuations due to adverse events occurred slightly numerically more frequently among inhaled insulin patients than among SQ patients, but occurred with equal frequency between inhaled insulin patients and patients in oral agent groups.
- As noted with Type 1 patients, a large number of patients were discontinued from study for "withdrawn consent" in the uncontrolled portions of Phase 2 and Phase 3 trials.

In controlled Phase 2 and Phase 3 studies in Type 1 diabetics, the most common category of events leading to discontinuation was respiratory, and all discontinuations due to respiratory adverse events occurred in inhaled insulin group patients (Section 7.1.3.2). When considering all Phase 2 and Phase 3 trials, both controlled and uncontrolled, respiratory events were again the most common category of adverse events leading to discontinuation, with a total of 21 (2.3%) of inhaled insulin group patients discontinuing due to respiratory AEs. Cough was the most common AE leading to discontinuation, accounting for 10 discontinuations (1.1% of all Ph 2/3 Type 1 patients).

In controlled Phase 2 and Phase 3 studies in Type 2 diabetics, the most common category of events leading to discontinuation was respiratory, and 26/28 discontinuations due to respiratory adverse events occurred in inhaled insulin group patients (Section 7.1.3.2). When considering all Phase 2 and Phase 3 trials, both controlled and uncontrolled, respiratory events were again the most common category of adverse events leading to discontinuation, with a total of 42 (3.9%) of inhaled insulin group patients discontinuing due to respiratory AEs. Cough was the most common AE leading to discontinuation, accounting for 26 discontinuations (1.6% of all Ph 2/3 Type 2 patients). Three events of oropharyngeal irritation (glossitis, gingivitis, pharyngitis) resulted in discontinuation in controlled Phase 2/3 trials in inhaled insulin patients, with one additional discontinuation due to pharyngitis in extension trials. No discontinuations due to oropharyngeal irritation occurred in SQ or oral agent control patients. In controlled Phase 2 and

Phase 3 trials in Type 2 diabetics, discontinuations due to neoplasia did not occur more frequently among inhaled insulin group patients than among control patients.

The large number of patients for whom consent was withdrawn was of concern to the clinical reviewer, because it raised the question of whether some of these patients actually dropped out for adverse events, tolerability issues, device use problems, or other noteworthy reasons (Section 7.1.3.1). Upon request, the applicant submitted further information regarding the actual wording that the patient or investigator gave as the reason for those discontinuations that were listed as due to "withdrawn consent", "patient no longer willing to participate in study" or "other". This information was not available for all patients. Most of these stated reasons did not relate to adverse events, tolerability issues, or device problems, but some did. When considering the group of those studies for which revised data for reasons for discontinuation were available, the apparently more frequent misclassification of discontinuation reasons among inhaled insulin patients than among comparator patients led to greater differences between groups in the rates of discontinuation for:

- adverse events (greater difference in frequency for both Type 1 and Type 2)
- insufficient clinical response (greater difference in frequency for Type 1)

If investigators were unclear on how reasons for discontinuation should have been classified, one would expect that they would have misclassified reasons with approximately equal frequency in inhaled insulin and control groups. However, discontinuations due to adverse events and insufficient clinical response appear to have been misclassified more frequently for inhaled insulin patients than for comparator patients in the controlled Phase 2/3 population (Section 7.1.3.1). This disparity in rates of apparent misclassification of reasons for discontinuation is unexplained, but raises a question of investigator reporting bias in this open-label development program.

Temporary discontinuations due to adverse events were more common among Type 1 inhaled insulin patients than among Type 1 patients in SQ groups (Section 7.1.3.1). For adult Type 1 patients in controlled Phase 2 and Phase 3 trials, 4.7% of inhaled insulin patients had temporary discontinuations due to adverse events, compared to 1.3% of SQ patients. The most common category of adverse events leading to temporary discontinuation among Type 1 diabetic inhaled insulin patients was respiratory, with 16 such events among inhaled insulin patients vs 1 such event in the SQ groups.

Temporary discontinuations due to adverse events were more common among Type 2 inhaled insulin patients (5.6% of patients) compared to Type 2 SQ group patients (1.6% of patients), but occurred with comparable frequency in patients in oral agent groups (6.8%) (Section 7.1.3.1). Again, the most common category of event leading to temporary discontinuation was respiratory, with 24 Type 2 subjects (1.9%) temporarily discontinuing inhaled insulin for respiratory reasons, vs 1 respiratory temporary discontinuation among SQ patients, and zero among oral agent patients. Temporary discontinuations due to hypoglycemia were also more common among Type 2 inhaled insulin patients, with 14 patients (1.1%) temporarily discontinuing due to hypoglycemia, vs 3 (0.6%) and 3 (0.5%) of SQ and oral agent patients, respectively. Temporary

discontinuations due to digestive events, particularly diarrhea, occurred more frequently among Type 2 oral agent group patients.

The incidences of new or worsening laboratory abnormalities did not appear to differ between inhaled insulin group patients and comparator patients (Section 7.1.7).

An intensive QTc study was not performed. From routine electrocardiograms from those studies for which postbaseline ECGs were obtained, mean changes in QTc were not significantly different between inhaled insulin and comparator patients in controlled Phase 2 and Phase 3 studies (Section 7.1.7.5.2). From routine electrocardiograms, outlier abnormalities of the QTc interval did not occur more frequently among inhaled insulin patients than among comparator patients in controlled Phase 2 and Phase 3 studies. Among adult Type 1 and Type 2 diabetics, there was little difference between groups for mean ECG changes in heart rate, PR interval or QRS width (Section 7.1.9.3).

Mean pulse and blood pressure did not change substantially from baseline to last observation for adult patients, and there were no significant differences between treatment groups (Section 7.1.8.3).

Type 2 patients who were insulin-using at study entry did not gain more weight with inhaled insulin than with comparator; in Study 108, SQ patients actually gained statistically significantly more weight (1.28 kg, 95% CI 0.6-1.96). However, inhaled insulin patients who were not using insulin at study entry did have statistically significantly greater weight gain than comparator patients in several studies (Section 7.1.8.3.1). The difference in weight gain was most evident in Study 1001, in which add-on inhaled insulin was compared to add-on metformin.

Study 1007 was a clinical pharmacokinetic and pharmacodynamic study conducted in 10 gestational and 3 pregestational diabetic women (Section 7.1.14). It was an open-label, randomized, two-period, two-treatment, crossover study. Each subject received a single morning fasting dose of either 9 U regular SQ insulin or 1 puff of 3 mg inhaled insulin, then no study insulin for 14 days (with continued usual management of their diabetes), then a single dose of cross-over study medication. Insulin Tmax was earlier with inhaled insulin administration than with regular SQ insulin. Cmax was 83% higher with inhaled insulin than with regular SQ. $AUC_{0\text{-}360}$ was similar for both treatments. Insulin Tmax in this study was similar to that seen in nonpregnant diabetics in other studies, where Tmax ranged from 38-78 minutes. Fasting insulin Cmax in these women was also similar to fasting insulin Cmax seen in nonpregnant diabetics. Bioavailability of inhaled insulin relative to SQ was 10% based on geometric mean; this relative bioavailability is similar to that seen in nonpregnant women. Time to maximum decline in glucose was somewhat shorter for pregnant inhaled insulin patients in this study (210 minutes) than for nonpregnant Type 2 diabetics receiving inhaled insulin in Study 1004, where the time to maximum decline in glucose was 248 minutes. The maximum decline in glucose concentration was less in these pregnant diabetics exposed to inhaled insulin than it was in nonpregnant Type 2 diabetics in study 1004, but significant differences in baseline glucose levels limit the interpretability of this observation.

Clinically apparent spontaneous abortions occur in insulin-requiring diabetic women at a rate roughly twice that of the normal population of pregnant women (29.5% vs 10-15%) (Miodovnik 1988). In the Exubera® development program, 4/10 women who became pregnant while taking inhaled insulin had a spontaneous abortion (Section 7.1.14). In Studies 106 and 107, mean end-of-study insulin antibody levels for Type 1 nonpregnant diabetic women were 32.6% binding (SD 22.46) for the semiquantitative Mayo assay, and 435.0 μU/mL (SD 1194.2) for the quantitative Esoterix® assay. None of the women in the development program who had adverse pregnancy outcomes had known insulin antibody levels higher than these means.

The information obtained about human reproductive risk of Exubera® is not substantial enough at this time to conclude that Exubera® can cause fetal harm, and thus Pregnancy Categories D or X are not warranted. However, some information is available in pregnant women which could assist clinicians in decision-making about whether or not to choose Exubera® for the treatment of pregnant women (Section 7.1.14). The clinical reviewer recommends the addition to the label of a summary of the known information about the pregnancy outcomes of women exposed to Exubera®.

Study 1004 was conducted in elderly (>65 years of age), obese Type 2 diabetics, and compared inhaled insulin (4 mg) PK and PD to that of SQ regular insulin (12 U) (6 mg inh ins or 18 U SQ for patients with weight ≥ 150 kg) (Section 8.3). The study did not include a control arm of younger patients. Inhaled insulin had an earlier insulin Tmax and a higher Cmax, but a similar exposure by $AUC_{0\text{-}360}$.

Data are insufficient for conclusions regarding the potential effect of Exubera® on growth.

Pharmacokinetic studies of inhaled insulin in hepatic and renal impairment were not submitted by the applicant.

Some data were submitted to characterize the use of inhaled insulin in COPD patients (Section 7.4.2.4). Study 1005 compared inhaled insulin PK between healthy patients and those with COPD. Following administration of 3 mg of inhaled insulin, Cmax was greater (by up to 50%) in COPD patients than in healthy subjects. Tmax occurred 25-50 minutes earlier in COPD patients compared to normal subjects. Overall insulin exposure ($AUC_{0\text{-}360}$) was greater in COPD patients than in healthy subjects (by approximately 15%). Bioavailability of inhaled insulin was 11% in healthy controls compared to 23-25% in COPD patients.

As of 1 Sep 04, four patients with COPD had died; one of these was taking inhaled insulin and died of metastatic colon cancer (Section 7.4.2.4). No asthma patients had died as of 1 Sep 04.

Hypoglycemia event rates did not differ between underlying lung disease patients (with COPD or asthma), and those without these disorders, for either inhaled insulin or comparator patients (Section 7.4.2.4). Patients with either asthma or COPD who were taking inhaled insulin appeared to experience asthenia more frequently than comparator patients (with or without underlying lung disease), and more frequently than inhaled insulin patients without underlying lung disease.

Otherwise, the small number of each type of event within the underlying lung disease groups precludes meaningful conclusions regarding other types of events.

Declines in FEV1 and DLco occurred more frequently among inhaled insulin patients than among control patients in the controlled Phase 2/3 population, and are further discussed in Dr. Seymour's pulmonary review. The clinical reviewer examined nonpulmonary adverse events in those patients who had significant declines in PFTs, defined as declines from baseline to last observation of ≥ 15% in FEV1, TLC or FVC, and/or ≥ 20% decline in DLco (Section 7.4.2.4). Hypoglycemia rates (by study definition of requirement for assistance, or BG value <36 mg/dL) were similar between patients who had significant PFT declines and those who did not, for both inhaled insulin and comparator patients. Hypoglycemia rates among patients who had declines in PFTs were similar between inhaled insulin and comparator patients. Reported adverse events of hypoglycemia occurred more commonly in inhaled insulin patients who had significant declines in PFTs than in comparator patients who had significant declines in PFTs [154/218 (70.6%) vs 86/154 (55.8%)], but at an equal rate to that seen in comparator patients who did not have significant declines in PFTs (1069/1512, 70.7%). Total cardiovascular events occurred at a higher rate in inhaled insulin patients who had a significant decline in PFTs (45/218, 20.6%) than in comparator patients who had a significant decline in PFTs (26/154, 16.9%) and comparator patients who did not have a significant decline in PFTs (202/1512, 13.4%). No single cardiovascular event occurred at a significantly higher rate among inhaled insulin patients who had significant declines in PFTs.

Tobacco smoking within six months prior to randomization was an exclusion criterion for Phase 2/3 studies. In clinical pharmacology studies (005, 016, 1003, 1020), inhaled insulin pharmacokinetics and pharmacodynamics were significantly different in smokers (Section 7.4.2.4). In nondiabetic and Type 2 diabetic smokers, Cmax, Tmax and AUC of inhaled insulin was 2-5 fold higher than that of nonsmokers. Smoking cessation led to a decline in insulin exposure within 3 days of abstinence, with further attenuation over time; by 7 days, insulin exposure was near that seen in nonsmokers. Resumption of smoking after abstinence resulted, within 2-3 days, in increased exposure similar to that seen prior to smoking cessation. The applicant is concerned about these findings, and considers the potential for rapid changes in systemic insulin exposure to be a prohibitive risk associated with cigarette smoking. The applicant recommends that patients should abstain from smoking for at least 6 months before inhaled insulin treatment, and should remain abstinent during inhaled insulin treatment. However, in order to reduce the likelihood that smokers will use inhaled insulin, specific education of patients and providers may be needed, with enhanced emphasis on the risk. Physicians may overlook the smoking statement in a long product label, and patients sometimes do not share their smoking history with their physicians.

Study 1005 included pharmacokinetic data regarding co-administration of inhaled insulin and inhaled albuterol (Section 7.4.2.5). While overall, inhaled insulin PK did not differ from 30 minutes pre- to 30 minutes post- albuterol, the small subset of emphysema patients (5/12 total COPD patients) had mean insulin exposure that was 46% higher post-albuterol than pre-albuterol.

Animal carcinogenicity and reproductive toxicity studies were not performed (Section 3.2). The lack of carcinogenicity data is a potential concern; insulin is a growth factor, and inhaled insulin appears to be a clinical lung irritant. Although no difference was noted between inhaled insulin and comparator groups for the incidence of lung carcinoma, the duration of study was shorter than the usual duration of time needed from an initial lung insult to the development of a malignancy. However, Dr. Alavi, the animal toxicology reviewer, states that it is unlikely that animal carcinogenicity studies would have resolved questions regarding human carcinogenic potential, due to problems administering the drug chronically via inhalation to rodents, and due to a potential nonrelevant tumorigenic response in rodents, which have insulin receptors in the lung.

9.1.3 Conclusions Regarding Dosage and Administration, Dose Equivalence, and Dose Proportionality

In the DOSAGE AND ADMINISTRATION section of the proposed product label, the applicant proposes a similar regimen to that used in clinical trials (Section 8.1). Administration 10 minutes prior to meals is proposed. Calculation of initial dosage based on body weight is proposed, with a formula: body weight (kg) x 0.05 mg, rounded down to nearest whole mg, = premeal dose, assuming 3 meals/day. The applicant does not propose instructions for transitioning from subcutaneous premeal insulin to inhaled insulin, based on the patient's current premeal subcutaneous insulin dose. No formula is presented for dosing by carbohydrate exchanges, and there are no recommendations for calculation of bedtime snack doses. The label does not include recommendations for titration increments. Mention is made of the fact that three 1 mg unit dose blisters cause greater insulin exposure than one 3 mg dose blister. The dosage and administration section does not mention a need for close monitoring by the patient and physician during initiation of inhaled insulin.

Initial dosage based on body weight is a reasonable approach. However, numerous patient factors may affect initial inhaled insulin requirement, including the patient's particular degree of insulin resistance, current glycemic control, hypoglycemia history, et al. These factors could result in significant under- or over- dosing if initial dose is based on weight alone. The proposed label makes mention of the need for consideration of factors other than weight in determining starting dose, but does not provide specific guidance. The potential consequences of initial under- or over- dosing could likely be managed by intensive monitoring by the patient and physician in the first few weeks of initiation of inhaled insulin; the clinical reviewer recommends the addition of this recommendation to the product label.

The applicant's proposed label states, in the DOSAGE AND ADMINISTRATION section, that Exubera® may be used during intercurrent respiratory illness, e.g. bronchitis, upper respiratory infection, and rhinitis. However, some differences in inhaled insulin pharmacokinetics and glucose pharmacodynamics were seen with rhinoviral challenge (Section 7.4.2.4). Analysis of the effect of acute bronchitis on insulin pharmacokinetics and post-inhaled-insulin glucose pharmacodynamics was not provided. The clinical reviewer recommends that the label state that the effect of intercurrent respiratory illness, such as acute bronchitis, upper respiratory infection, and rhinitis, has not been fully evaluated, and that careful monitoring of blood glucose during

intercurrent respiratory illness is recommended. The clinical reviewer also recommends that patients be advised to have subcutaneous insulin and needles available for use during intercurrent respiratory illness, in case glucose control proves difficult with inhaled insulin during that time.

Dose proportionality and dose equivalence were not demonstrated for Exubera® (Sections 5.1 and 8.1).

In Study A2171012, dose proportionality was not demonstrated over a range of doses (Sections 5.1 and 8.1). In this study, dose proportionality of several dosages was compared, including doses of 1 mg (1x1 mg), 2 mg (2x1 mg), 3 mg (1x3 mg), 4 mg (1x3 mg + 1x1 mg) and 6 mg (2x3 mg). None of the 90% confidence intervals for any AUC comparison fell within bioequivalence boundaries (80-125%).

When examining the actual individual subject data from the trial, one notes that multiple samples obtained for insulin Cmax and AUC for 3 mg dosing had lower values than the mean seen for 2 mg dosing (Section 8.1). For Cmax, 10/29 samples obtained for Cmax at the 3 mg dose fell below the mean Cmax for the 2 mg dose. In this study, each patient generally only received 3 of the 5 dose combinations. A total of 6 patients received both the 2 mg dose and the 3 mg dose (doses given at different times during study). Among these 6 patients (each of whom had 2 Cmax values recorded for each dose), 4/6 had a Cmax value for the 3 mg dose that was lower than a Cmax value for the 2 mg dose. A total of 6/26 samples for the 6 mg dose had lower Cmax values than the mean for the 4 mg dose, and 2/6 patients who received both the 4 mg dose and the 6 mg dose had a Cmax value for the 6 mg dose that was lower than a Cmax value for the 4 mg dose. Similar findings were noted for AUC at each time interval, as illustrated in Table 8.1.2.

Based on this study (and in Study 1006 described below), it appears that the possibility exists that, in a given patient, the titrated "increase" from 2x1 mg to 1x3 mg could actually result in lower blood insulin AUC, rather than the expected increase in blood insulin (Sections 5.1 and 8.1). This could create a significant problem in upward titration of dose, particularly in the lower dosage ranges such as might be used in Type 1 diabetes. This problem would be magnified if the drug is used off-label for the treatment of pediatric Type 1 diabetics, who generally have lower body weights and therefore smaller initial insulin doses.

Dose equivalence was also not demonstrated for three 1 mg blisters and one 3 mg blister (Sections 5.1 and 8.1). In Study 1006, the AUC_{0-360} for 3 inhalations of 1 mg was approximately 40% higher than that for 1 inhalation of 3 mg, and Cmax was approximately 30% higher. This difference appears to be related in part (but not entirely) to a problem with the inhaler; it is much more efficient in breaking up the powder in blisters of a lower fill mass. Although the overall percent emitted mass is fairly similar for 3x1 mg and 1x3 mg, the 1 mg strength emits a higher proportion of particles <3.3 μM, which the applicant asserts is the particle size most capable of reaching the deep lung, and the particle size associated with optimal systemic absorption. However, the relative difference in fine particle dose for the 1 mg blister vs the 3 mg blister does not entirely account for the dose nonequivalence. In addition to the potential problems noted above with titration, patients must be instructed not to substitute three 1 mg inhalations for one 3

mg inhalation if they run out of their 3 mg blisters. This could result in greater insulin exposure and risk for hypoglycemia.

This particular drug-device combination exhibits marked variability in emitted mass of dry powder insulin; this variability significantly exceeds previously established limits for dry pulmonary inhalers (Section 3.1). This variability in delivered dose is concerning, because it may result in an increased risk for hypoglycemia when doses significantly above the mean are delivered.

While variability in delivery of insulin with Exubera® is a concern, it is noteworthy that marked variability in absorbed dose of insulin, and pharmacodynamic response, is also a major concern with subcutaneous insulin, and is well-described in the medical literature. Within this development program, significant variability in pharmacodynamic (glucose) response was seen for both inhaled and subcutaneous insulin, and the variability was comparable in standardized meal studies (Section 8.1).

9.2 Recommendation on Regulatory Action

Not applicable at this time.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Not applicable at this time.

9.3.2 Required Phase 4 Commitments

Not applicable at this time.

9.3.3 Other Phase 4 Requests

Not applicable at this time.

9.4 Labeling Review

Not applicable at this time.

9.5 Comments to Applicant

Not applicable at this time.

10 APPENDICES

10.1 Review of Individual Study Reports

Not applicable; see Section 6.

10.2 Line-by-Line Labeling Review

Not applicable at this time.

10.3 DMEDP Response to DDMAC Tradename Objection

The following memo was entered into the DFS archive on 13 May 05 in response to an objection by the Division of Drug Marketing and Advertising to the applicant's proposed tradename:

MEMORANDUM TO FILE

6 May 05
To: David Orloff, MD, Division Director, Division of Metabolic and Endocrine Drug Products
From: Karen Murry Mahoney MD, Medical Officer, Division of Metabolic and Endocrine Drug Products (DMEDP)
Re: NDA 21868 Exubera® inhaled insulin, DMEDP response to request by Division of Drug Marketing and Advertising (DDMAC) for comment on DDMAC tradename objection

Pfizer has submitted a New Drug Application for their inhaled insulin product, for which they plan to use the tradename "Exubera®". DDMAC recently notified Pfizer of an objection by DDMAC to the name, as "overly fanciful and promotional". Mr. Brian Green of Pfizer Regulatory Affairs notified Dr. Oluchi Elekwachi, DMEDP Project Manager for Exubera®, that Pfizer plans to challenge the DDMAC objection. DDMAC has asked DMEDP to comment on whether DMEDP agrees with DDMAC's objection to the tradename. This memorandum documents the DMEDP Medical Officer Reviewer's opinion regarding the tradename objection, using the regulation upon which the DDMAC objection is based [21 CFR § 202.1(a)(3)].

The pertinent regulation, accessed via the Tarius United States Code of Federal Regulations database on 6 May 05, reads as follows:
"§ 202.1 Prescription-drug advertisements.
(a)…
(3) The advertisement shall not employ a fanciful proprietary name for the drug or any ingredient in such a manner as to imply that the drug or ingredient has some unique effectiveness or composition, when, in fact, the drug or ingredient is a common substance, the limitations of which are readily recognized when the drug or ingredient is listed by its established name.
..."

The medical officer can understand DDMAC's concern, in that the "fanciful" name implies an "exuberant" response. However, the medical officer can also see that Pfizer could reasonably argue that the remainder of the regulatory statement limits the objectionability of a fanciful name to those circumstances in which the drug is not substantially different from other products containing the same active ingredient. While Exubera® contains insulin, a common drug, its characteristics are not limited to those seen with injected insulin. If it is approved, its different route of administration, and the painfree nature of that administration route, will make this product substantially different

from injected insulin. The fact that Exubera® contains insulin will not be hidden, either in labeling or promotion. The applicant would have no reason at all to create confusion about the fact that Exubera® contains insulin. Additionally, Pfizer specifically asked the Agency about the acceptability of the name years ago (17 Dec 99), and in writing, was notified on 4 Oct 00 that the Office of Postmarketing Risk Assessment expressed no objection to the proposed tradename Exubera®. Thus, Pfizer tried long ago to make sure that FDA found the name acceptable before Pfizer progressed further.

The medical officer is not familiar with how the "overly fanciful" clause has been applied by DDMAC in the past, and realizes that FDA has to apply interpretation of this clause fairly across all companies' drug naming plans. However, to the medical officer's reading of the regulation, the name of this particular drug does not seem objectionable enough to require the company to expend time and resources to change the name and marketing campaign plans. Additionally, the applicant made a good faith effort years ago to seek the Agency's input regarding the proposed tradename.

In summary, the DMEDP medical officer's opinion is that the proposed tradename Exubera® does not violate 21 CFR § 202.1(a)(3), and the medical officer's lack of objection to the proposed tradename is further supported by the applicant's previous good faith efforts to seek Agency input regarding the acceptability of the tradename.

10.4 Serious Adverse Event Listings by Patient

The following tables list serious adverse events by patient. Separate tables are provided for adult Type 1, adult Type 2, and pediatric patients. Separate tables are also provided by treatment group. In constructing these tables of serious adverse events by patient, the clinical reviewer extracted data from the applicant's Table 6.3.1.1 from the applicant's Summary of Clinical Safety, pages 1903-2296. This table did not assign an organ system for events, and therefore organ systems were assigned by the clinical reviewer and may differ from what the applicant would have assigned. When a patient was reported to have had a severe hypoglycemic event with possibly related events that occurred at the same time, such as seizures or injury, the clinical reviewer assigned the organ system as "Metabolic". In reviewing these events, the clinical reviewer also noted some dates of adverse events that could not be reconciled with the length of studies, e.g. SAEs occurring at >2 years for a 6 month study. This was brought to the attention of the applicant, and corrected data were provided for 45 events. The tables below include the corrected data. If the reader attempts to compare the following tables to the applicant's original table, dates of adverse events may differ due to this later correction by the applicant. These tables relate to Section 7.1.2 of the review, and are numbered accordingly.

Table 7.1.2.1.1
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Trials in Adult Type 1 Diabetics
Sorting by Patient
Treatment = Inhaled Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Patient ID	Age (yrs)	Gender	Dose[1] (mg)	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
102E	5002	0003	27	F	27	1275	Metab	Diabetic ketoacidosis		
102E	5002	0084	52	F	8	474	Repro/ Uro	Bilateral torsion of hydrosalpinges, pelvic adhesions, cystic masses of ovaries and fallopian tubes		
102E	5005	0044	34	F	9	1093	GI	Food poisoning	Mentioned in narrative for decline in FEV1, FVC, DLco	
102E	5005	0108	45	M	20	1845	Cardiac	Triple vessel coronary artery disease		
						1854	Cardiac	Congestive heart failure		
						1910	Nervous	Transient ischemic episode		
102E	5006	0053	47	F	7	823	Repro/ Uro	Excessive intermittent menstruation		
102E	5007	0068	40	M	18	1414	General	Noncardiac chest pain		
102E	5007	0070	56	M	10	557	GI	Cholelithiasis, cholecystitis	Mentioned in narrative for pneumonia	
102E	5007	0106	57	M	23	1073	Cardiac	Acute myocardial infarction	Ischemic heart disease	y (death)
102E	5008	0066	57	M	11	2073	Cardiac	Coronary artery blockage		
102E	5011	0077	35	F	5	1378	Accid/ Inj	Automobile accident	same	y (death)
102E	5012	0035	34	M	7	57	Musculoskel	Back pain		
102E	5013	0013	25	M	10	345	Accid/Inj	Laceration thumb		
102E	5013	1008	44	M	9	196	Metab	Diabetic ketoacidosis		
106	5008	6168	55	F	19	6	Uro	Worsening stress incontinence		
106	5030	6881	36	M	27	99	Metab	Hyperglycemia, inadvertent overdose of inhaled insulin, hypoglycemia, convulsions, unconsciousness		
106	5030	6883	53	F	31	7	Metab	Hypoglycemia, unconscious, hypothermia	same	
106	5044	6275	23	M	18	136 (12)	Metab	Diabetic ketoacidosis		
106	5060	6966	36	M	39	33	Metab	Hypoglycemic coma		y
107	5029	7597	53	M	10	141	Eye	Left eye hemorrhage		
107	5052	7181	53	M	13	23	Metab	Severe hypoglycemic event, motor vehicle accident	same	
107	5063	7419	34	M	27	67	GI	Chronic gastritis		
107	5127	7221	30	F	6	18	Metab	Hypoglycemia, grand mal seizure	same	
111[6]	5005	7683	36	F	8	536	Accid/ Injur	Dog bite hand, cellulitis	Not mentioned in narrative for discontinuation due to frequent hypoglycemia	

Table 7.1.2.1.1
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Trials in Adult Type 1 Diabetics
Sorting by Patient
Treatment = Inhaled Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Patient ID	Age (yrs)	Gender	Dose[1] (mg)	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
						789	Metab	Not in applicant's SAE table	Increasingly frequent hypoglycemia (from narrative)	y
111	5005	7686	54	M	4	313	GI	Abdominal pain		
111	5008	6669	50	F	9	689 (11)	Metab	Hypoglycemia	Also MVA (11 d after last inh ins)	
111	5010	7615	41	F	15	252	Infec	Appendicitis		
111	5010	8105	50	F	24	288	Vasc	Carotid stenosis		
					20	245	Cardiac	Worsening coronary artery disease		
111	5013	6604	46	F	8	190	Neoplasms	Breast cancer		
111	5016	6929	26	M	20	316	Musculoskel	Torn ligament left shoulder	Mentioned in narrative for decline in DLco	
111	5025	6590	24	F	12	493	Metab	Ketoacidosis		
111	5025	6592	44	M	24	509	Metab	Hypoglycemia	also convulsions	
					31	558	Metab	Hypoglycemia, seizure	same	
111	5025	6593	45	M	21	850 (183)	Cardiac	Heart attack		
111	5029	7597	55	M	22	804	GI	Cholecystitis		
111	5029	7599	58	F	3	863	Musculoskel	Torn rotator cuff	Mentioned in narrative for change in HRCT	
					4	224	Proc Comp	Postoperative surgical site hematoma	Mentioned in narrative for change in HRCT	
					3	741	Musculoskel	Adhesive capsulitis shoulder	Mentioned in narrative for change in HRCT	
111	5029	7602	34	M	18	366	Infec	Appendicitis		
111	5030	6883	56	F	14	862 (unk)	Infec	Worsening sinusitis	Mentioned in narrative for high ins Ab	
					14	862 (51)	Heme	Anemia	Mentioned in narrative for high ins Ab	
					12	111	Metab	Hypoglycemic event, unresponsiveness	same	
					17	92	Metab	Hypoglycemia, altered level of consciousness	same	
111	5036	7117	36	M	9	45 (11)	Accid/ Injur	Accidental fall, epidural hematoma, right-sided hemiparesis	Not mentioned in narrative for hypoglycemia	
111	5041	7153	67	M	36	916	Cardiac	Worsening of angina		
111	5042	6713	42	M	9	118	Accid/ injur	Accidental fall, broken leg	same; also had fractured sternum	

Table 7.1.2.1.1
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Trials in Adult Type 1 Diabetics
Sorting by Patient
Treatment = Inhaled Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Patient ID	Age (yrs)	Gender	Dose[1] (mg)	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
									in MVA on day 66	
111	5045	6229	53	M	36	547	Cardiac	Coronary artery disease	Mentioned in narrative for decline in FEV1	
111	5047	6555	40	F	17	652	Infec	Influenza	Mentioned in narrative for high ins Ab	
111	5049	6245	33	M	13	64	Neuro	Seizures		
111	5049	6767	46	M	13	591	Infec	Osteomyelitis, chronic left foot ulcer		
111	5049	6770	54	F	14	329	Cardiac	Myocardial infarction	same	y (death)
111	5049	6772	32	F	3	679	Repro/ Uro	Worsening menorrhagia		
111	5025	5682	62	M	24	734 (168)	Neuro	Delirium of unknown etiology		
					18	492	Metab	Severe hypoglycemia		
111	5052	7180	34	M	7	103	Metab	Hypoglycemia, incoherent speech	same	
111	5053	6782	35	M	18	168	GI	Nausea, vomiting		
					18	168	Metab	Dehydration		
111	5053	6783	54	M	20	576	Cardiac	Angina pectoris		
					11	392	Musculoskel	Left shoulder pain		
111	5055	6622	57	M	21	77 (85)	Metab	Severe hypoglycemic event, unconsciousness	Not mentioned in narrative for decline in FEV1 and DLco	
111	5056	7711	51	M	5	710	Cardiac	Worsening unstable angina	Mentioned in narrative for hi ins Ab	
111	5059	6681	37	F	12	452	GI	Exacerbation cholelithiasis		
111	5060	6960	37	M	18	5	Neuro	Convulsions		
111	5061	7793	44	F	12	727	Metab	Hypoglycemia	Hypoglycemia, unconsciousness	y (10 days later)
111	5061	7794	30	F	16	146	Accid/ Injur	Left wrist fracture, accidental fall	Mentioned in narrative for hypoglycemia	
					26	303	Metab	Hypoglycemia, unconsciousness, incontinence	same	
					27	314	Metab	Hypoglycemia	same	
111	5061	7797	46	M	15	480	Metab	Hypoglycemic event, unconsciousness	same	
111	5066	7741	41	F	30	323	Metab	Hypoglycemic seizure	same	
111	5066	7745	29	M	13	190	Metab	Hypoglycemia, seizure	same	
111	5070	6896	30	F	42	137	Metab	Hypoglycemia	Hypoglycemia, unresponsiveness	

Table 7.1.2.1.1
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Trials in Adult Type 1 Diabetics
Sorting by Patient
Treatment = Inhaled Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Patient ID	Age (yrs)	Gender	Dose[1] (mg)	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
111	5070	6898	42	F	5	304	Metab	Hypoglycemia, seizure	same	
111	5072	6819	38	F	12	642	Infec	Spontaneous bacteremic illness		
111	5075	7328	35	M	16	279	Infec	Right ear infection	Ear infection not mentioned in narrative for decline in FEV1	
111	5076	7227	42	M	9	489	Metab	Diabetic ketoacidosis		
111	5076	7230	47	F	9	121	Accid/ Injur	Accidental fracture right ulna		
					5	194	Infec	Breast abscess		
111	5081	6446	18	F	12	230	Metab	Hypoglycemic episode	same	
111	5098	7071	19	F	7	870	Infec	Gastroenteritis	Mentioned in narrative for decline in DLco	
111	5127	7221	31	F	12	486	Metab	Hypoglycemia, seizure	same	
					12	522	Metab	Hypoglycemia, seizure	same	
					12	527	Metab	Hypoglycemia, seizure	same	
					18	615	Metab	Recurrent hypoglycemia, recurrent seizure	same	
					15	632	Metab	Recurrent hypoglycemia, recurrent seizure	same	y
111	5127	7224	60	M	15	667	Metab	Hypoglycemic event	Hypoglycemia, unconsciousness	
A2171022	1001	0003	23	F	8	241	Metab	Diabetic ketoacidosis		
A2171022	1001	0007	39	M	5	54	Eye	Worsening macular degenerative disease left eye		
A2171022	1001	0009	37	M	11	197	Metab	Hypoglycemic reaction, unconsciousness	same	y
A2171022	1006	0302	37	M	10	31	Metab	Hypoglycemia	Hypoglycemia, motorcycle accident, clavicular rhegma	
					10	192	Metab	Hypoglycemia	same	
A2171022	1006	0319	34	M	13	347	Cardiac	Angina		
A2171022	1007	0361	19	F	9	504	Infec	Pyelonephritis		
A2171022	1007	0364	22	F	8	307	Repro/ Uro	Renal colic		
A2171022	1010	0537	48	M	21	315	GI	Gastroenteritis	same	
						215	Metab	Hypoglycemia		
A2171022	1015	0837	37	M	8	83	Metab	Hypoglycemia, loss of consciousness	same	
A2171022	1016	0891	51	M	10	227	Cardiac	Myocardial infarction		y (death)
A2171022	1017	0949	29	M	7	409	Metab	Diabetic ketoacidosis	Not mentioned in narrative for decline in DLco and	

Table 7.1.2.1.1
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Trials in Adult Type 1 Diabetics
Sorting by Patient
Treatment = Inhaled Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Patient ID	Age (yrs)	Gender	Dose[1] (mg)	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
									discontinuation from study due to cough	
A2171022	1019	0068	34	F	6	31	Metab	Hypoglycemia, loss of consciousness		
A2171022	1020	1131	35	F	6	1	General	Chest pain		
A2171022	1025	1424	32	M	12	244	Metab	Hypoglycemia, seizure	same	
A2171022	1026	1485	47	F	8	531	Accid/ injur	Trimalleolar fracture right ankle		
A2171022	1026	1489	22	F	20	482	Metab	Hypoglycemia	Hypoglycemia, motor vehicle accident	
A2171022	1029	1661	35	M	12	89	Metab	Hypoglycemia	same	
A2171022	1030	1722	56	F	12	440	Cardiac	Recurrence of paroxysmal supraventricular tachycardia		
A2171022	1031	1785	20	F	12	170	Infec	Kidney infection		
A2171022	1031	1188	62	M	14	125	Infec	Abdominal cellulitis at surgical site		
							Procedural complications (Proc comp)	Ventral and umbilical herniae		
A2171022	1031	1788	62	M	15	316	Infec	Right rotator cuff wound infection, worsening chronic shoulder pain		
					15	570	General	Chest pain		
A2171022	1033	1899	62	M	12	474	Accid/ Injur	Dislocated right trimalleolar ankle fracture		
A2171022	1037	2136	51	F	8	15	Metab	Hypoglycemia, loss of consciousness	same	
A2171022	1037	2140	52	M	6	300	Accid/ injur	Motorcycle accident, multiple lacerations		
A2171022	1039	2253	22	F	7	284	Repro/ Uro	Preterm labor	same	
						284	Metab	Ketoacidosis	same	
A2171022	1050	3914	46	M	12	3	Metab	Hypoglycemia	same	
					21	162	Metab	Hypoglycemic event	same	
					21	165	Metab	Hypoglycemic event	same	
A2171022	5074	3082	51	M	21	4	Metab	Hypoglycemia	same	
A2171022	5096	3140	43	F	2	167	GI	Gallbladder lithiasis		
A2171022	5098	3258	47	F	7	105	Neoplasm	Carcinoma left breast	Lobular breast carcinoma in situ	

Table 7.1.2.1.1
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Trials in Adult Type 1 Diabetics
Sorting by Patient
Treatment = Inhaled Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Patient ID	Age (yrs)	Gender	Dose[1] (mg)	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
A2171022	5147	3376	45	F	15	89	Metab	Recurrent hypoglycemic episodes		
A2171022	5152	3622	48	F	13	54	Cardiac	Myocardial infarction	same	y (death)
A2171022	5155	3735	41	F	5	Not reported (NR)	Eye	Cataract left eye		
					7	331	Repro/ Uro	Spontaneous abortion		
A2171026	1001	0017	50	F	6	10	Metab	Hypoglycemia	same	
A2171026	1001	0005	33	M	14	10	Metab	Hypoglycemia		
					9	58	Metab	Hypoglycemia		

Includes Studies 1001, 1002, 1005, 1007, 1009, 1017, 1022, 1026, 1027, 1028, 1029, 102E, 103, 1030, 1036, 104, 104E, 106, 107, 108, 109, 110, 111
1 Dose at time of adverse event
2 Duration of exposure in days at time of event. If event occurred after discontinuation, the number of days after discontinuation is included in parentheses
3 Applicant's assigned term
4 Term used by investigator or patient; nb- applicant provided SAE narratives only for pulmonary SAEs and SAEs that led to death or discontinuation
5 If patient withdrew due to this adverse event, noted with a "y"
6 For Study 111, an extension of several clinical trials, it was not clear from the applicant's Table 6.3.1.1 whether a patient had Type 1 or Type 2 diabetes. Readers who wish to examine the source Table 6.3.1.1 can tell what type of diabetes the patient had by looking at the 5th number of the patient's identification number in the applicant's Table 6.3.1.1. If this number was a zero, 1 or 8, the patient had Type 2 diabetes. If it was any other number, the patient had Type 1 diabetes (telephone communications with Mr Brian Green, Pfizer Regulatory Affairs, 31 Mar 05 and 6 Apr 05)
Source: Applicant's Table 6.3.1.1, Section 2.7.4, pgs 1903-2296.

Table 7.1.2.1.2
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 1 Diabetics
Sorting by Patient
Treatment = SQ Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Pt ID	Age	Gender	Dose[1] (U/day)	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
106	5014	6805	56	M	Regular 8	14	Musculoskel	Herniated disc		
106	5019	6141	53	M	Regular 41	7	Skin	Heel infection		
106	5025	6592	42	M	Regular 59	51	Metab	Severe hypoglycemia, convulsions, confusion, expressive aphasia	same	

Table 7.1.2.1.2
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 1 Diabetics
Sorting by Patient
Treatment = SQ Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Pt ID	Age	Gender	Dose[1] (U/day)	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
106	5030	6882	43	M	Regular 25	488	Metab	Hypoglycemia, altered mental status	same	
106	5040	6572	63	F	Regular 7	122	Neuro	Syncope	same	
						122	Cardiac	Sinus arrhythmia, sinus tachycardia	same	DCed from inh ins in Study 111 extension, for recurrent severe hypoglycemia
106	5049	6767	43	M	Regular 22	65	Musculoskel	Fracture foot, sprain ankle		
106	5049	6771	41	F	Regular 21	40	Cardiac	Unstable angina		
					Regular 15	131	Neuro	Seizure		
106	5051	6869	54	M	Regular 6	77	Musculoskel	Increased back pain, bulging spinal discs		
106	5065	6947	22	F	Regular 27	17	Metab	Hypoglycemia, seizure, intentional overdose of study drug	Also tongue-biting with airway obstruction	
					Regular dose unknown	147	GI	Gastroenteritis		
						147	Metab	Ketoacidosis		
107	5027	7735	35	M	Regular 18	45	Metab	Hypoglycemia, loss of consciousness, bicycle accident, facial and knee lacerations, short term memory loss, decreased ability to concentrate	same	
107	5061	7797	45	M	Regular 21	40	Metab	Severe hypoglycemic event, memory loss		
107	5095	7488	18	F	Regular 31	46	GI	Gastrointestinal illness, vomiting		
107	5103	7240	24	F	Regular 24	133	General	Chest pain		
A2171022	1008	0438	47	M	Lispro 19	209	Metab	Hypoglycemia, seizure	same	
					Lispro 17	600	Infec	Chronic meningitis	Not mentioned in narrative for hypoglycemia	
A2171022	1008	0447	29	F	Regular 12	478	Repro/ Uro	Premature labor (after drug exposure to fetus)		
A2171022	1012	0654	64	F	Lispro 27	491	Cardiac	Coronary artery disease		
A2171022	1013	0713	47	F	Lispro 39	306	Skin	Diabetic ulcer toe		
A2171022	1016	0897	55	M	Aspart 18	385	Cardiac	Coronary artery disease		
A2171022	1021	1185	42	F	Aspart 35	184	Neoplasm	Bilateral breast cancer	same	

Table 7.1.2.1.2
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 1 Diabetics
Sorting by Patient
Treatment = SQ Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Pt ID	Age	Gender	Dose[1] (U/day)	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
A2171022	1021	1187	36	F	Lispro 39	355	Psych	Worsening of depression		
					Lispro 51	604	Psych	Worsening of depression		
					Lispro 48	701	Psych	Recurrent depression, suicidal ideation		
A2171022	1021	1190	51	M	Aspart 25	49	GI	Recurrent peptic ulcer		
					Aspart 34	351	Skin	Cellulitis right leg		
A2171022	1023	1306	20	F	Aspart 38	Not reported	Repro/ Uro	Pregnancy		y
					Aspart 52	677	Metab	Severe hypoglycemic event, diabetic seizure		
A2171022	1024	1371	56	F	Aspart 60	244	Metab	Hypoglycemia, acute change in mental status	same	
A2171022	1025	1426	31	F	Regular 42	176	Metab	Hypoglycemia, loss of consciousness		
A2171022	1028	1605	38	F	Lispro 21	348	Neoplasm	Uterine leiomyoma		
A2171022	1029	1665	49	M	Lispro 9	117	Metab	Hypoglycemia, loss of consciousness	same	
					Lispro 14	273	Psych	Exacerbation of depression	Mentioned in narrative for hypoglycemia	
					Lispro 17	330	Psych	Worsening of depression	Mentioned in narrative for hypoglycemia	
A2171022	1036	2075	36	M	Aspart 32	551	Metab	Hypoglycemia, loss of consciousness	same	
A2171022	1037	2135	29	M	Lispro 23	32	Metab	Hypoglycemia	Hypoglycemia, fall	
					Lispro 15	532	Metab	Hypoglycemia	same	
A2171022	1037	2138	48	F	Lispro 16	105	Metab	Hypoglycemic reaction, syncope	same	
A2171022	1037	2145	53	M	Lispro 25	183	Infec	Appendicitis		
A2171022	1038	2192	49	M	Lispro 32	502	Metab	Hypoglycemia, seizure	same	
					Lispro 31	704	Metab	Hypoglycemic event, loss of consciousness	same	
					Lispro 32	727	Metab	Hypoglycemia, loss of consciousness	same	
A2171022	1038	2193	50	M	Lispro 30	374	Metab	Hyperglycemia		
					Lispro 30	390	General	Diaphoresis with mild exertion		
A2171022	1039	2254	29	F	Lispro 6	444	Eye	Retinal detachment		
A2171022	1043	2489	58	M	Lispro 22	16	Neoplasm	Malignant pancreatic tumor	same	y
A2171022	1049	2843	41	F	Lispro 7	189	Metab	Hypoglycemia	same	
A2171022	1049	2847	37	M	Lispro 36	189	Metab	Hypoglycemia, seizure	same	
A2171022	1050	3913	37	M	Lispro 27	354	Metab	Hypoglycemic event, seizure	same	
A2171022	1050	3915	23	F	Regular 30	218	Metab	Hypoglycemic event	same	

Table 7.1.2.1.2
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 1 Diabetics
Sorting by Patient
Treatment = SQ Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Pt ID	Age	Gender	Dose[1] (U/day)	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
A2171022	5060	2904	41	M	Lispro 5	8	Metab	Hypoglycemic, loss of consciousness	same	
A2171022	5060	2907	45	F	Aspart 54	374	Psych	Major depression		
A2171022	5074	3081	27	F	Lispro 29	171	Infec	Appendicitis		
A2171022	5090	3210	36	F	Lispro 8	457	Neoplasm	Worsening of colonic polyposis		
A2171022	5138	3316	29	M	Lispro 8, Regular 12	8	Metab	Hypoglycemia	same	
A2171022	5138	3319	39	F	Lispro 59	38	Metab	Hypoglycemic episode, loss of consciousness	same	
					Lispro 45	668	Metab	Hypoglycemic episode	same	
A2171022	5147	3375	42	M	Lispro 21	122	Metab	Hypoglycemic reaction, unconsciousness	same	
A2171022	5147	3380	35	M	Lispro 22	313	Infec	Influenza		
A2171022	5152	3620	52	M	Lispro 24	677	Metab	Hypoglycemia, loss of consciousness	same	
A2171022	5154	3680	36	M	Lispro 60	42	Metab	Hypoglycemic event		
A2171028	1042	4077	38	F	Lispro 31	108	Resp	Exacerbation of asthma	same	
A2171030	1004	0099	64	F	Aspart 20	315	GI	Bowel obstruction, Crohn's disease	same	y
						315	Cardiac	Non-ST segment (sic) myocardial infarction	same	

Includes Studies 1001, 1002, 1005, 1007, 1009, 1017, 1022, 1026, 1027, 1028, 1029, 102E, 103, 1030, 1036, 104, 104E, 106, 107, 108, 109, 110, 111
1 Dose at time of adverse event
2 Duration of exposure in days at time of event. If event occurred after discontinuation, the number of days after discontinuation is included in parentheses
3 Applicant's assigned term
4 Term used by investigator or patient; nb- applicant provided SAE narratives only for pulmonary SAEs and SAEs that led to death or discontinuation
5 If patient withdrew due to this adverse event, noted with a "y"
Source: Applicant's Table 6.3.1.1, Section 2.7.4, pgs 1903-2296

Table 7.1.2.1.3
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = Inhaled Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Patient ID	Age (yrs)	Gender	Dose[1]	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	W/D?[5]
103	5002	0095	43	F	18	67	Musculoskel	Surgical removal of spinal rods and screws		
103	5014	0022	64	M	18	84	Nervous	Cerebral vascular accident	same	y
						84	Cardiac	Bradycardia, premature ventricular contractions	same	
103E	5002	0003	53	M	18	298	Vasc	Femoral artery blood clot		
103E	5002	0010	42	M	21	1022	Cardiac	Coronary artery disease	same	y
103E	5002	0089	62	M	1	1741	Vasc	Cerebrovascular accident	same	y
103E	5002	0089	61	M	6	1403	Cardiac	Chest pain		
					1	1707	Vasc	Intracranial bleeding		
103E	5002	0092	58	F	20	344	Cardiac	Congestive heart failure	Mentioned in narrative for decline in FEV1 and DLco, and renal insuff	
					18	1580	Renal	Not in listing	End-stage renal disease	y
					18	998	Heme	Exacerbation of chronic anemia	Mentioned in narrative for decline in FEV1 and DLco, and renal insuff	
					24	1227	Resp	Bronchitis	Mentioned in narrative for decline in FEV1 and DLco, and renal insuff	
					24	1227	Cardiac	Congestive heart failure	Mentioned in narrative for decline in FEV1 and DLco, and renal insuff	
103E	5002	0094	50	F	12	716	GI	Gangrenous cholecystitis		
103E	5005	0063	59	F	6	172	Resp	Pneumonia	same	
					6	172	Accid/ Inj	Syncope	Syncope while driving, MVA	
103E	5005	0069	60	M	3	397 (16)	Cardiac	Pericardial effusion	same	
					3	397 (42)	Infec	HIV+, Hep B	same	y
					3	397 (16)	Resp	Bilateral pleural effusions	same	
103E	5006	0047	45	F	18	38	Metab	Hypokalemia	Not mentioned in narrative for decline in DLco	
103E	5006	0048	60	M	21	469	Musculoskel	Hip replacement surgery	Not mentioned in death narrative	
					27	934	Cardiac	Acute myocardial infarction	Mentioned in death narrative	
103E	5008	0041	65	F	12	501	Cardiac	Coronary artery disease		
					12	700	Cardiac	Worsening coronary artery disease		
					19	804	Cardiac	Chest pain		
					10	1063	Cardiac	Unstable angina		
103E	5010	0071	64	M	13	1082	Cardiac	Acute myocardial infarction		
103E	5013	0012	48	M	18	40 (14)	GI	Gastroenteritis	Not mentioned in narrative for d/c due to decline in DLco	
103E	5013	0013	54	F	9	2	Cardiac	Chest pain	Not mentioned in narrative for d/c due to restrictive ventilatory defect and decline in DLco	
103E	5014	0023	66	M	18	666	Vasc	Transient ischemic attack		
103E	5014	0024	55	M	24	796	Skin	Toe ulcer		
					30	1659	Infec	Infection of surgical amputation site second toe		

Table 7.1.2.1.3
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = Inhaled Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Patient ID	Age (yrs)	Gender	Dose[1]	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	W/D?[5]
103E	5014	0030	59	M	6	2027	Cardiac	Restenosis stent	Mentioned in narrative for shortness of breath	
					33	2094	Cardiac	Chest pain	Mentioned in narrative for shortness of breath	
					33	2094	Resp	Shortness of breath	same	
					24	502	Resp	Shortness of breath	same	
					24	502	Cardiac	Coronary artery disease	Mentioned in narrative for shortness of breath	
					24	1332	Cardiac	Worsening coronary artery disease	Mentioned in narrative for shortness of breath	
104E	5002	0073	46	F	13	458	Repro/ Uro	Uterine fibroids		
104E	5005	0068	65	F	4	297	Cardiac	Coronary artery disease	Mentioned in narrative for declines in FVC, FEV1, and DLco	
					4	351	Cardiac	Worsening coronary artery disease	Mentioned in narrative for declines in FVC, FEV1, and DLco	
					4	660	Musculoskel	Distal radial fracture	Not mentioned in narrative for declines in FVC, FEV1, and DLco	
					10	808	Cardiac	Coronary artery disease	Mentioned in narrative for declines in FVC, FEV1, and DLco	
104E	5005	0071	56	F	5	106	Neoplasms	Breast adenocarcinoma		
104E	5006	0018	64	M	9	829	Cardiac	Myocardial infarction		
104E	5006	0019	63	M	4	863	Cardiac	Myocardial infarction		
104E	5010	0058	55	M	7	1249	Resp	Acute inhalation injury due to sulfuric acid		
104E	5010	0061	57	M	24	586	Musculoskel	Laminectomy		
104E	5011	0034	69	M	24	1748	GI	Elevated liver enzymes, jaundice		
					12	430	Cardiac	Ischemic heart disease, aortic stenosis		
					8	479	GI	Multiple duodenal ulcers, upper GI bleed		
					14	570	GI	Diverticulosis		
					3	701	GI	Diverticulitis		
					3	739	Repro/ Uro	Benign prostatic hypertrophy		
104E	5011	0040	63	M	9	1881	Cardiac	Chest pain		
104E	5014	0049	62	M	21	1122	Cardiac	Coronary artery disease		
					18	1227	Cardiac	Acute congestive heart failure		
104E	5016	0002	47	F	36	874	Repro/ Uro	Worsening ovarian cyst		

Table 7.1.2.1.3
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = Inhaled Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Patient ID	Age (yrs)	Gender	Dose[1]	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	W/D?[5]
104E	5016	0004	54	M	24	248	GI	Colonic impaction		
104E	5016	0005	65	M	24	952	Cardiac	Acute myocardial infarction	same	y (death)
104E	5016	0006	65	M	4	1216	Neuro	Paraplegia	same	y
104E	5016	0007	63	M	13	1772	Cardiac	Cardiopulmonary arrest	same	y (death)
104E	5016	0010	52	M	30	1243	Cardiac	Coronary occlusion		
108	5010	8003	75	M	9	116	Neoplasm	Esophageal cancer, progression of cancer, liver metastases, gastrointestinal bleeding	same	y (death)
108	5020	8087	58	M	21	172	Skin	Foot ulceration, foot cellulitis		
108	5024	8493	68	F	13	171	Skin	Diabetic bullosis	Mentioned in narrative for decline in DLco	
108	5026	8345	55	M	18	21	Cardiac	Worsening coronary artery disease	Mentioned in narrative for decline in FEV1 and DLco; underwent CABG same day	
108	5024	8133	65	M	30	65	Repro/ Uro	Impotence		
108	5043	8113	49	M	35	144	Musculoskel	Pinched back nerve, left hip pain, capsulitis left shoulder	Capsulitis mentioned in narrative for decline in PFTs	
						144	Infec	Urinary tract infection	Not mentioned in narrative for decline in PFTs	
108	5048	8119	48	M	24	65	GI	Esophageal bleed	same	y (death)
108	5051	8555	56	F	19	70	Cardiac	Unstable angina		
108	5055	8537	63	M	45	44	Cardiac	Worsening coronary artery disease	Mentioned in narrative for later DC due to pulmonary edema	
108	5060	8092	49	M	20	143	GI	Pancreatitis		
108	5060	8097	73	M	29	43	Cardiac	Congestive heart failure	Mentioned in narrative for decline in PFTs and bronchitis	
						43	Resp	Bronchitis	same	
108	5099	8038	39	M	10	54	Skin	Worsening foot ulcers	Mentioned in narrative for abnormal chest X-ray	
108	5138	8144	57	M	10	107	Musculoskel	Hip fracture	Mentioned in narrative for decline in FVC and DLco	
109	5042	0475	56	F	20	16	Cardiac	Acute myocardial infarction, unstable	Mentioned in narrative for	

Table 7.1.2.1.3
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = Inhaled Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Patient ID	Age (yrs)	Gender	Dose[1]	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	W/D?[5]
								angina	discontinuation due to cough, and decline in PFTs	
109	5043	0031	65	F	18	75	Resp	Shortness of breath		y
						75	Skin	Ankle edema		
109	5044	0348	46	M	33	34	Cardiac	Chest pain		
109	5051	0737	56	M	27	18	Cardiac	Atypical angina		
109	5053	0354	42	M	33	71	Psych	Situational depression		
					39	83	Skin	Lower extremity cellulitis		
109	5071	0483	66	M	21	12	Metab	Hypoglycemic event		
111[6]	5002	0056	50	M	8	478	Neoplasm	Prostate adenocarcinoma		
111	5002	0447	70	M	13	42	Cardiac	Chest pain, coronary artery disease		
111	5002	8589	50	M	18	421	Cardiac	Myocardial infarction		
111	5005	8067	52	M	12	111	Musculoskel	Cervical bone spur	Event not in narrative for decline in PFTs	
						435	Resp	Not in applicant's Table 6.3.1.1	Bronchitis, 19% decline in total lung capacity, 23% decline in DLco (from narrative)	y
111	5005	8443	61	M	5	600	Vasc	Dry gangrene toe		
					10	715	Infec	Osteomyelitis toe		
111	5007	8044	64	M	8	839	GI	Hiatal hernia, chest pain		
					7	20	Cardiac	Chest pain		
					7	31	Vasc	Bilateral carotid artery stenosis		
					10	233	Vasc	Hypertension		
111	5008	1012	74	F	7	781	Cardiac	Angina attack		
					9	298	Musculoskel	Herniated disc		
111	5010	8105	49	F	21	245	Cardiac	Worsening coronary artery disease		
111	5013	0068	54	F	69	248	Metab	Thyroid nodule	Not mentioned in narrative for decline in FVC	
111	5014	0389	57	M	24	328	Cardiac	Worsening coronary artery disease		
					24	470	Cardiac	Worsening coronary artery disease		
111	5014	0393	57	M	36	217	Cardiac	Worsening coronary artery disease		
					36	668	Musculoskel	Torn rotator cuff		
111	5016	8053	65	M	9	683	Musculoskel	Guillain Barre syndrome	Mentioned in narrative for HRCT and CXR findings	

Table 7.1.2.1.3
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = Inhaled Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Patient ID	Age (yrs)	Gender	Dose[1]	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	W/D?[5]
111	5016	8054	78	F	6	486	GI	Gastroenteritis	Mentioned in narrative for decline in DLco	
111	5016	8065	72	M	16	874	Repro/ Uro	Hematuria		
111	5017	8450	73	M	14	469	Metab	Hypoglycemia, car accident	same	
111	5020	0244	63	F	14	576	General	Chest pain		
111	5022	1389	55	F	12	184	Accid/ Injur	Automobile accident, cervical spinal cord compression		
111	5024	0129	45	M	45	954 (112)	Metab	Obesity	Not mentioned in narrative for atelectasis and pneumonia	
					45	954 (116)	Resp	Atelectasis left lung	same	
					24	420	Cardiac	Chest pain	Mentioned in narrative for atelectasis and pneumonia	
					30	679	Infec	Pneumonia	same	
					30	756	GI	Cholecystitis	Mentioned in narrative for atelectasis and pneumonia	
111	5025	8021	51	M	18	582	Neoplasm	Basal cell carcinoma		
111	5025	8413	53	M	18	686 (43)	Neuro	Hydrocephalus		
					18	686 (133)	Neuro	Chronic bilateral subdural hematoma		
111	5026	0599	55	M	30	285	GI	Upper abdominal pain		
111	5026	0601	60	M	13	391	Cardiac	Coronary artery disease		
111	5028	0694	54	M	14	12	Cardiac	Coronary ischemia, coronary blockage	Mentioned in narrative for discontin due to cough; pt had PTCA	
111	5029	0336	41	M	26	678	Musculoskel	Ruptured disc		
111	5029	0436	67	F	17	747	Metab	Hyponatremia		
						747	General	Chest pain		
111	5029	0437	57	M	20	618	Neuro	Cerebrovascular accident	same	y
111	5029	1495	56	M	3	27	Cardiac	Worsening left chest pain, coronary artery disease		
111	5029	8371	58	M	28	728 (194)	Cardiac	Myocardial infarction	Not mentioned in narrative for decline in FVC	
					35	615	GI	Duodenal ulcer, esophagitis	Mentioned in narrative for decline in FVC	
111	5029	8421	68	F	19	498	Musculoskel	Worsening osteoarthritis left knee		
					19	634	Heme	Deep vein thrombosis		
					19	730	Musculoskel	Decreased range of motion knee		

Table 7.1.2.1.3
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = Inhaled Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Patient ID	Age (yrs)	Gender	Dose[1]	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	W/D?[5]
111	5030	0616	61	M	31	1001 (71)	Infec	Pneumonia	same	
					30	439	Cardiac	Mitral valve regurgitation, multivessel coronary artery disease	Mentioned in narrative for pneumonia	
					30	498	Cardiac	Atrial fibrillation, atrial flutter	Not mentioned in narrative for pneumonia	
					30	696	Cardiac	Angina	Not mentioned in narrative for pneumonia	
111	5030	0617	58	M	19	447	GI	Pancreatitis, acute cholecystitis		
111	5030	8354	57	M	16	413	Infec	Cellulitis		
111	5030	8356	44	M	10	15	GI	Constipation	Not mentioned in narrative for hypoglycemia and MVA- see event in Study 111	
					10	15	Musculoskel	Mechanical low back pain	Not mentioned in narrative for hypoglycemia and MVA- see event in Study 111	
111	5031	0089	51	M	9	403	Cardiac	Inferior myocardial infarction		
					9	403	Neuro	Left arm paresthesia		
111	5031	0508	56	M	9	686	Repro/ Uro	Kidney stone		
111	5031	0512	43	M	12	143	Musculoskel	Bone spurs back		
111	5034	0366	75	M	12	1011	Cardiac	Worsening ischemic heart disease		
					13	321	Vasc	Right carotid artery occlusion		
111	5034	0368	64	M	51	229	Musculoskel	Spinal stenosis		
111	5034	1006	73	M	13	331	GI	Gastric ulcer, duodenal ulcer		
					13	334	Musculoskel	Exacerbation or arthritis hip		
111	5034	8035	68	M	30	727	Cardiac	Myocardial infarction, coronary artery disease	same	y
111	5034	8462	68	M	12	346	Cardiac	Worsening coronary artery disease		y
111	5040	8445	72	F	12	888	Neoplasm	Renal cell carcinoma		
					9	97	Neoplasm	Papillary thyroid carcinoma		
					9	97	Metab	Primary hyperparathyroidism		
111	5040	8446	75	F	15	583	Neoplasm	Endometrial carcinoma		
					19	552	Musculoskel	Worsening degenerative joint disease		
111	5040	8448	76	M	17	15	Vasc	Carotid stenosis	Mentioned in narrative for decline in DLco	

Table 7.1.2.1.3
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = Inhaled Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Patient ID	Age (yrs)	Gender	Dose[1]	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	W/D?[5]
111	5041	8024	62	M	17	256	Neoplasm	Cancer	Metastatic colon cancer	y
					15	789	Skin	Diabetic foot ulcer		
111	5041	8487	61	M	15	598	Cardiac	Coronary blockage		
					15	221	Skin	Worsening diabetic foot ulcer		
111	5042	0070	52	M	39	364	Vasc	Deep vein thrombosis		
111	5042	0476	58	M	19	718	General	Sarcoidosis	same	y
111	5042	0477	56	F	12	315	General	Chest pain	Mentioned in narrative for decline in DLco	
111	5042	8002	74	M	21	510	Neoplasm	Extranodal lymphoma	same	y
					21	510	Musculoskel	Pathological fracture	same	
111	5042	8479	62	M	8	95	Proc Comp	Postsurgical complication suture rupture	Mentioned in narrative for decline in FEV1	
						95	Cardiac	Inferior wall myocardial infarction	Mentioned in narrative for decline in FEV1	
111	5043	0394	72	M	12	350	Neoplasm	Prostate carcinoma		
111	5043	0395	45	F	6	625 (8)	Psych	Suicidal depression		
					4	249	Psych	Depression		
					4	267	Musculoskel	Disc herniation, worsening lower back pain		
					9	508	Musculoskel	Decreased left shoulder mobility		
111	5043	8113	50	M	36	133	Infec	Abscess of amputation stump	Not mentioned in narrative for decline in PFTs	
					36	266	Cardiac	Acute myocardial infarction	Mentioned in narrative for decline in PFTs	
					41	483	Cardiac	Worsening coronary artery disease	Mentioned in narrative for decline in PFTs	
111	5043	8547	61	M	8	60 (1)	Cardiac	Congestive heart failure, chest pain		y
111	5044	8013	73	M	12	669	Poisoning	Hyperammonemia, suspected selenium toxicity, altered mental status, acute renal failure, congestive heart failure	same	y
						669 (4)	Poisoning	Multiorgan failure	same	y (death)
111	5044	8364	53	F	9	26	Repro/ Uro	Kidney stone		
111	5045	1383	47	M	18	463	Cardiac	Congestive heart failure, coronary artery disease, possible pulmonary edema	mentioned in narrative for incr ins Ab and decline in DLco	y

Table 7.1.2.1.3
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = Inhaled Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Patient ID	Age (yrs)	Gender	Dose[1]	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	W/D?[5]
111	5045	8089	66	M	7	377	Musculoskel	Left shoulder pain, torn rotator cuff		
111	5046	0484	61	M	21	138	Infec	Pneumonia	same; also decline in DLco	
111	5046	8336	76	M	22	920	Cardiac	Acute myocardial infarction, cardiac arrest, worsening coronary artery disease	same; also had decline in DLco	y (death)
111	5048	0041	71	M	16	44	Neoplasm	Encapsulated fibrosarcoma	Not mentioned in narrative for decline in DLco	
					9	122	Cardiac	Unstable angina	Mentioned in narrative for decline in DLco	
111	5040	0042	48	M	40	70	Accid/ Injur	Temporary paralysis lower extremities, motor vehicle accident		
111	5048	0412	63	M	11	97	Cardiac	Coronary artery disease	Mentioned in death narrative	
					6	589	Accid/ Injur	Blunt force trauma to head and face while on coumadin, cerebral hemorrhage	same	y (death)
111	5048	0414	73	M	6	240	Cardiac	Acute myocardial infarction	same	y (death)
111	5048	0496	78	M	18	239	GI	Elevated liver function tests, elevated bilirubin, obstructive biliary tract disease		y
111	5048	8120	54	F	18	581	Cardiac	Congestive heart failure	Mentioned in narrative for decline in DLco	
					18	729 (132)	Resp	Shortness of breath	Mentioned in narrative for decline in DLco	
					16	166	Cardiac	Congestive heart failure	Mentioned in narrative for decline in DLco	
111	5048	8403	76	M	18	685 (85)	Vasc	Transient cerebral ischemia	Not mentioned in narrative for change in end-of-study HRCT	
					13	48	Vasc	Ischemic bowel, thrombosis of mesenteric artery	Not mentioned in narrative for change in end-of-study HRCT	
					13	62	Cardiac	Congestive heart failure, atrial fibrillation	Not mentioned in narrative for change in end-of-study HRCT	
					13	106	Renal	Acute renal insufficiency, hematuria, hyperkalemia	Not mentioned in narrative for change in end-of-study HRCT	
					13	106	Heme	Worsening anemia		
111	5048	8428	57	M	12	222	Cardiac	Angina		
111	5048	8609	69	F	16	588	Infec	Urinary tract infection	Not mentioned in narrative for decline in FEV1 and DLco	

Table 7.1.2.1.3
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = Inhaled Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Patient ID	Age (yrs)	Gender	Dose[1]	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	W/D?[5]
					7	4	Cardiac	Non-Q-wave myocardial infarction	Mentioned in narrative for decline in FEV1 and DLco	
111	5048	8610	54	F	18	675 (169)	Resp	Shortness of breath	same; also decline in DLco	
					24	305	Cardiac	Exertional angina	Not mentioned in narrative for dyspnea and decline in DLco	
111	5049	0119	50	F	10	6	Cardiac	Recurrent chest pain, worsening coronary artery disease		
111	5049	0570	68	F	6	12	Metab	Hyponatremia		
					7	603	Heme	Iron deficiency anemia		
					7	603	Renal	Renal insufficiency		
111	5049	0573	65	M	8	346	Cardiac	Atrial fibrillation		
111	5049	8378	67	M	15	722 (5)	Cardiac	Worsening coronary artery disease	same	y
111	5051	0737	58	M	41	478	Musculoskel	Carpal tunnel syndrome	Mentioned in narrative for decline in DLco	
111	5052	1007	52	M	28	817	Cardiac	Coronary artery disease	Mentioned in narrative for decline in PFTs	
					28	905	GI	Pancreatitis	Mentioned in narrative for decline in PFTs	
111	5053	0010	59	F	19	905 (147)	Neoplasm	Merkel cell carcinoma		
					25	381	Cardiac	Coronary artery disease		
111	5053	0353	65	M	18	84	Resp	Abnormal pulmonary function test	Worsening pulmonary function	y
111	5053	0354	42	M	39	29	Infec	Recurrent right leg cellulitis		
					13	134	Skin	Exacerbation of bilateral foot ulcers		
111	5054	8381	54	M	18	359	Cardiac	Myocardial infarction		
111	5055	0581	70	M	44	717	Cardiac	Exacerbation of congestive heart failure	same	y
111	5055	8537	65	M	54	356	Resp	Pulmonary edema	same; reason for discontinuation changed from original reason of pulm edema to nonserious decrease in pulm function	y
111	5058	1078	65	M	7	113	Infec	Cellulitis right leg		
111	5060	0664	56	M	19	49	Cardiac	Acute myocardial infarction	same	
					19	98	Cardiac	Acute myocardial infarction	same	y
111	5060	0665	70	M	34	234	Infec	Pneumonia	same	
111	5060	0672	73	M	21	658	Cardiac	Myocardial infarction	same	
					21	658	Neoplasm	Rectal tumor	Malignant rectal tumor	y

Table 7.1.2.1.3
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = Inhaled Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Patient ID	Age (yrs)	Gender	Dose[1]	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	W/D?[5]
					21	663 (29)	Cardiac	Recurrent myocardial infarction	same	
111	5060	8041	68	M	54	218	Musculoskel	Left knee pain	Mentioned in narrative for pneumonia and decline in DLco	
111	5060	8062	55	M	20	79	Proc Comp	Worsening of incisional hernia		
111	5060	8110	53	M	22	562	Cardiac	Unstable angina	same; underwent CABG	y
111	5062	0641	70	M	8	1	Musculoskel	Increased worsening of rotator cuff tendonitis		
111	5062	0642	49	M	41	282 (22)	Cardiac	Coronary artery disease	same	
					41	181	Resp	Worsening pulmonary function tests	same	
111	5069	8393	69	F	13	99	Infec	Infected left knee prosthesis		
					13	99	Proc Comp	Left knee reconstruction		
					16	350	Cardiac	Recurrent atrial fibrillation, congestive heart failure		
111	5070	0721	62	M	5	871	Cardiac	Exacerbation atrial fibrillation	Mentioned in narrative for decline in FEV1	
111	5070	0721	60	M	5	212	Eye	Left eye vitreous hemorrhage		
					5	47	Cardiac	Recurrent atrial fibrillation		
					5	269	Cardiac	Recurrent atrial fibrillation		
					4	363	Cardiac	Recurrent atrial fibrillation		
					5	234	Cardiac	Recurrent atrial fibrillation		
111	5070	8031	48	M	30	829	Resp	Respiratory distress	same	y
					20	279	Infec	Perianal abscess	Not mentioned in narrative for resp distress	
111	5071	0073	69	F	8	561	Neoplasm	Bowel tumor, signet ring cell carcinoma	Mentioned in narrative for decline in TLC	
					8	691	Neoplasm	Anemia, neutropenia, bacterial cellulitis left hand IV site, chemotherapy	Mentioned in narrative for decline in TLC	
111	5071	8405	71	M	9	838	Infec	Cellulitis	Not mentioned in narrative for decline in PFTs and pneumonia	
111	5071	8406	74	F	9	669	Vasc	Transient ischemic attack	Mentioned in narrative for decline in DLco	
111	5071	8429	70	M	12	758	Cardiac	Coronary artery stenosis		
111	5072	0504	55	M	30	1072	Neoplasm	Cancer large intestine	Mentioned in narrative for decline in DLco	
111	5072	0507	73	M	5	478	Vasc	Ruptured cerebral hemorrhage,	same	y

Table 7.1.2.1.3
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = Inhaled Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Patient ID	Age (yrs)	Gender	Dose[1]	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	W/D?[5]
								subarachnoid hemorrhage, subdural hematoma		
					5	478 (7)	Vasc	Vasospasm, pulmonary emboli	same	
					5	478 (7)	Infec	Pneumonia	same	
111	5072	8072	49	F	9	72 (11)	Accid/ injur	Accidental fall, contusions		
					9	72 (11)	Vasc	Acute vein thrombophlebitis left leg, left femoral line		
111	5073	0542	65	F	10	512	GI	Cholelithiasis	Mentioned in narrative for decline in DLco	
111	5073	0562	64	F	23	229	Neoplasm	Breast cancer		
111	5073	8039	63	F	17	716	Neuro	Nerve root compression	Not mentioned in narrative for decline in DLco	
111	5073	8571	60	F	18	52	Cardiac	Recurrent sinus tachycardia		
					18	379	GI	Sialolithiasis		
111	5073	8572	61	M	12	159	Cardiac	Non-Q wave myocardial infarction		
					12	178	Cardiac	Acute coronary syndrome		
					12	251	Cardiac	Possible unstable angina		
					13	338	Cardiac	Probable ischemic heart episodes		
					16	477	Musculoskel	Broken leg		
111	5073	8585	72	F	18	775 (74)	Cardiac	Angina attack	Mentioned in narrative for decline in DLco	
					18	350	Cardiac	Unstable angina	Mentioned in narrative for decline in DLco	
111	5074	0110	65	M	13	167	GI	Subacute intestinal obstruction	Mentioned in narrative for bronchitis	
					13	167	Repro/ Uro	Left renal calculus, left hydronephrosis	Mentioned in narrative for bronchitis	
					13	167	Infec	Chronic pyelonephritis	Mentioned in narrative for bronchitis	
					32	353	Infec	Acute bronchitis	same	
111	5076	0700	65	M	19	336	Cardiac	Myocardial infarction	same	y
					19	336	Cardiac	Aortic valve stenosis	same	
111	5099	8038	40	M	24	149	Infec	Cellulitis left leg		
111	5112	1465	76	F	7	344	Neoplasm	Hamartoma right upper lobe lung		
111	5113	1013	46	M	24	520	Infec	Pneumonia		
111	5114	1022	71	M	10	662	Neoplasm	Prostate cancer		y
111	5116	1059	60	M	18	516	Neoplasm	Urothelial carcinoma		
111	5123	0796	55	F	11	403	Infec	Facial cellulitis		

Table 7.1.2.1.3
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = Inhaled Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Patient ID	Age (yrs)	Gender	Dose[1]	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	W/D?[5]
111	5127	0161	43	M	18	86	Accid/ Injur	Fracture left wrist, accidental fall	Mentioned in narrative for d/c due to cough	
111	5127	0652	65	F	3	217	Eye	Detached retina right eye		
111	5127	0655	65	M	14	249	Musculoskel	Worsening arthritis		
					11	544	Neuro	Syncope		
111	5127	0656	72	M	12	432	Neoplasm	Squamous cell lung carcinoma	same	y
111	5129	0219	52	M	18	100	GI	Abdominal pain		
111	5131	1074	62	F	36	229	Accid/ Injur	Hemothorax, fall from horse	Mentioned in narrative for decline in FEV1	
111	5134	1051	58	F	9	609 (78)	Resp	Restrictive lung disease	same	
A2171001	0004	0025	63	M	20	307	Cardiac	Acute myocardial infarction, ventricular tachycardia, ventricular fibrillation, congestive heart failure	same	y (death)
						307	Infec	Pneumonia, sepsis	same	
A2171001	0004	3014	56	F	7	275	Neuro	Transient ischemic attack		
					7	328	Cardiac	Chest pain		
A2171001	0005	1029	49	M	18	351	Neoplasm	Vocal cord polyp	same	
A2171001	0005	1030	45	F	45	294 (137)	Resp	Asthma attack	same	
						294 (137)	Cardiac	Chest pain	same	
A2171001	0005	0031	37	F	8	132	Cardiac	Unspecified chest pain		
A2171001	0011	0041	62	F	7	141	GI	Biliary lithiasis		
A2171001	0015	1051	72	F	21	157	Cardiac	Angina pectoris		
A2171001	0018	1058	56	F	16	224	Musculoskel	Rheumatoid arthritis		
A2171001	0035	1076	62	F	17	207	Neoplasm	Basal cell carcinoma of skin		
A2171001	0045	3036	77	F	9	366 (1)	Neuro	Syncope		
						366 (1)	Heme	Anemia		
A2171001	0046	3370	57	M	12	298	GI	Inguinal hernia		
A2171001	0056	0124	63	M	14	371	GI	Hernia inguinalis		
A2171001	0059	0135	62	M	3	175 (14)	Neoplasm	Urticaria	same	y
						175 (14)	Neoplasm	Urothelium carcinoma	no narrative	
A2171001	0060	1138	58	M	12	64	Cardiac	Abnormal treadmill test		
A2171001	0079	0178	63	F	13	470	Neoplasm	Colon carcinoma	no narrative	
A2171001	0090	1198	67	F	8	84	Vasc	Hypotension		
A2171001	0090	0198	64	F	9	330	Neoplasm	Gastric cancer	no narrative	

Table 7.1.2.1.3
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = Inhaled Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Patient ID	Age (yrs)	Gender	Dose[1]	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	W/D?[5]
A2171001	0093	1209	64	M	9	109	Cardiac	Left anterior descending artery stenosis	same	
A2171001	0096	0219	76	M	7	154	Accid/ Injur	Motor vehicle accident, concussion, forehead wound		
A2171001	0110	1243	56	M	23	186	Accid/ Injur	Fractured right heel		
A2171001	0134	1373	66	M	4	13	Cardiac	Myocardial infarction, acute cardiac failure	same	y
A2171001	0138	0278	70	F	5	379	Musculoskel	Coxarthrosis		
A2171001	0140	0303	58	F	15	228	Vasc	Segmental stenosis of left internal carotid		
A2171001	0141	3051	50	M	13	734	Cardiac	Myocardial infarction		
A2171001	0143	3084	63	F	36	532	Accid/ Injury	Fracture right arm		
A2171001	0145	1305	57	F	39	770	Cardiac	Acute myocardial infarction		
A2171001	0145	0305	52	M	32	240	Infec	Acute appendicitis, gangrene appendix		
A2171002	0002	7337	69	M	9	673	Accid/ Injur	Fall	Fall, head trauma, loss of consciousness	y
A2171002	0004	5025	53	M	9	3	Infec	Herpes zoster		
						3	Musculoskel	Ruptured disc		
A2171002	0005	6031	47	F	20	559	Vasc	Arterial hypertension		
A2171002	0005	6032	42	M	3	177	Cardiac	Palpitations		
A2171002	0037	6061	65	M	9	431	Cardiac	Acute myocardial infarction		
A2171002	0037	6062	55	M	15	396	Cardiac	Unstable angina	same	
					15	180	Infec	Bronchopneumonia	same; also decline in FEV1	
A2171002	0043	6002	53	F	4	44	Repro/ Uro	Disturbance of micturition		
A2171002	0043	6003	62	M	24	435	Eye	Cataract		
A2171002	0047	7051	59	M	12	44	GI	Elevated gamma glutamyl transferase		
A2171002	0049	7354	58	F	9	522	Metab	Hypothyroidism		
A2171002	0054	5106	69	M	7	582	Vasc	Hypertensive crisis		
A2171002	0056	1002	56	M	9	440	GI	Acute incarceration inguinal hernia		
A2171002	0067	5125	67	M	18	864	Repro/ Uro	Nephritic colic		
A2171002	0074	5149	62	M	11	338	Neuro	Facial paralysis		
A2171002	0074	6149	53	M	7	563	Repro/ Uro	Renal colic		
A2171002	0085	5171	68	M	10	242	Cardiac	Recurrent tachyarrhythmia	Tachycardia mentioned in narrative for decline in FEV1 and FVC	
					12	175	Cardiac	Cardiac insufficiency, worsening of	Cardiomegaly mentioned in narrative	

Table 7.1.2.1.3
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
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Trial	Center	Patient ID	Age (yrs)	Gender	Dose[1]	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	W/D?[5]
								coronary artery disease	for decline in FEV1 and FVC	
A2171002	0089	5183	70	M	9	253	Musculoskel	Thoracalgia		
A2171002	0108	5285	64	M	12	455	Neuro	Transient ischemic attack		
A2171002	0119	5234	50	M	12	209	Musculoskel	Calf pain		
A2171002	0119	5236	67	M	11	666	Neoplasm	Metastatic bronchial carcinoma	same	y
A2171002	0131	5262	54	F	14	289	Infec	Pneumonia	same	
A2171002	0133	6266	64	M	12	228	Resp	Pneumothorax	Event not mentioned in bronchial carcinoma narrative	
					11	676	Neoplasm	Metastatic bronchial carcinoma	same	
A2171002	0131	5262	54	F	14	289	Infec	Pneumonia		
A2171002	0141	7398	64	M	16	481	Musculoskel	Bunion		
A2171002	0141	7429	62	M	21	267	Vasc	Arterial hypertensive crisis, epistaxis	Hypertensive crisis not mentioned in narrative for decreased FEV1	
A2171002	0141	8038	75	F	9	671	Neoplasm	Duodenal carcinoma		
A2171002	0141	8060	70	F	12	638	Neoplasm	Chronic myelogenous leukemia		
						726	Neoplasm	Blast cell crisis		y
A2171002	0141	8376	46	F	11	15	Metab	Cushing Syndrome suspect		
A2171002	0142	7373	64	M	8	448	Vasc	Cerebellar ischemic vascular accident	Mentioned in narrative for decline in DLco	
A2171002	0142	8044	63	M	3	600	GI	Inguinal hernia		
A2171002	0142	8380	70	M	12	25	GI	Acute biliary pancreatitis	same	
A2171002	0143	8030	56	M	9	191	Cardiac	Coronary artery disease	Event not mentioned in narrative for decline in DLco; arterial thrombosis mentioned for Study Days 204-209	y
A2171007	5141	0006	29	F	3	1 (5)	Repro/ Uro	Prolapsed umbilical cord- baby, pregnant pregestational diabetic	same	y
						1 (28)	Neuro	Sagittal sinus thrombosis		
A2171017	1002	1008	66	M	45	124	General	Atypical chest pain		
A2171017	1003	1001	61	M	57	199	Accid/ Injur	Fall		
A2171017	1022	1003	51	F	10	289	Repro/ Uro	Unable to void		
							Metab	Worsening panniculus		
A2171017	1028	1005	34	M	32	235	Infec	Pneumonia		
A2171017	1030	1001	55	F	22	107	General	Weakness		
					27	174	Musculoskel	Musculoskel chest pain		

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Trial	Center	Patient ID	Age (yrs)	Gender	Dose[1]	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	W/D?[5]
A2171017	1031	1009	70	M	18	28	Cardiac	Congestive heart failure, pulmonary edema		y
A2171017	1040	0181	59	F	21	143	Neuro	Stroke		
A2171017	1062	1004	64	F	34	64	Skin	Left leg cellulitis		
A2171017	1062	1007	49	M	32	51	Cardiac	Increased heart rate		
					57	115	Cardiac	Coronary artery disease		
A2171017	1075	0391	55	F	36	30	GI	Nausea, vomiting		
						30	Neuro	Dizziness		
A2171027	1016	0648	49	M	3	90	Cardiac	Myocardial infarction	Myocardial infarction after hypoglycemic episode	y (death)
A2171027	5148	1329	43	M	13	6	Metab	Hypoglycemic episode, loss of consciousness	same	
A2171029	1006	1607	53	F	4	671	Vasc	Exacerbation of worsening hypertension		
A2171029	1010	0374	60	F	15	114	Cardiac	Atypical chest pain, coronary artery disease		
					12	174	Psych	Exacerbation bipolar disorder		
A2171029	1017	0541	63	M	14	211	Neuro	Neuritis		
A2171029	1019	1730	62	M	21	95	GI	Obstructed bile duct		
A2171029	1021	0607	58	M	8	271	Infec	Appendicitis		
A2171029	1025	1904	60	M	16	523	Cardiac	Multivessel coronary artery disease		
						528	GI	Partial small bowel obstruction		
A2171029	1025	1913	65	F	11	258	Resp	Asthma exacerbation	same	y
A2171029	1026	0659	61	M	22	226	Neoplasm	Colon carcinoma with metastases to kidney, liver, pancreas, lung	same	y (death)
A2171029	1038	0847	63	M	12	339	Accid/ injur	Torn tendon right knee, accidental fall		
A2171029	1041	0897	57	M	18	432	Renal	Acute renal failure, hyperkalemia		
A2171029	1043	2257	46	F	19	533	GI	Acute cholecystitis, abdominal pain		
A2171029	1043	2260	57	M	14	123	Infec	Cellulitis	Mentioned in narrative for incr ins Ab	
A2171029	1044	0958	74	M	20	460	Cardiac	Non-Q wave myocardial infarction		
					20	550	General	Noncardiac chest pain		
					19	709	Vasc	Orthostatic hypotension		
A2171029	1044	0960	53	F	16	583	Musculoskel	Lumbar spondyloradiculopathy		
A2171029	1045	2319	68	M	4	21	Resp	Bronchospasm NOS, hypersensitivity NOS	Acute bronchospasm, "questionable" allergic reaction to inhaled insulin	y
A2171029	1048	2495	51	M	18	364	Neoplasm	Prostate cancer		

Table 7.1.2.1.3
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
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Trial	Center	Patient ID	Age (yrs)	Gender	Dose[1]	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	W/D?[5]
A2171029	1049	2554	52	F	9	11	Infec	Right tonsil abscess		
A2171029	1057	4388	63	F	9	184	Proc comp	Posthysterectomy adhesions	Mentioned in narrative for bronchitis	
					15	476	Proc Comp	Posthysterectomy adhesions		
					12	218	Resp	Acute bronchitis	same	
A2171029	1059	2607	45	M	13	224	Metab	Hypoglycemic episode, seizure	same	
						138	Allerg	Allergic reaction to fexofenadine	Not mentioned in narrative for hypoglycemic episode	
A2171029	1069	1258	45	M	19	525	Infec	Infected fire ant bite		
A2171029	1069	1261	67	M	18	148	Infec	Diverticulitis		
A2171029	1069	1266	55	M	30	417	Neuro	Transient ischemic attack		
A2171029	1069	1280	52	M	30	180	Neuro	Migraine		
A2171029	1073	3086	66	M	7	514	Cardiac	Recurrent arrhythmia		
A2171029	1075	1371	53	M	20	65	Infec	Bacterial osteomyelitis right foot		
A2171029	1075	1373	70	M	9	394	Neuro	Transient global amnesia		y
A2171029	1075	1375	48	F	9	299	Neuro	Left Bell's palsy		
A2171029	1078	1490	58	M	12	16	Cardiac	Coronary artery blockage		
A2171029	1079	3260	69	M	15	225	Infec	Osteomyelitis, worsened back pain		y
A2171029	1081	3381	62	M	18	431	Infec	Urinary tract infection		
A2171029	1081	3384	38	M	18	556	Musculoskel	Muscle pain in back	Not mentioned in narrative for hypoglycemia and seizure	
A2171029	1081	3387	45	M	17	359	Resp	Bronchitis	same	
A2171029	1081	3390	58	F	15	333	Cardiac	Myocardial infarction		
A2171029	1083	3442	56	F	8	156	Cardiac	Myocardial infarction, hypotensive episode		
A2171029	1084	3497	48	M	18	279	Infec	Bilateral lower extremity cellulitis		
A2171029	1085	3552	51	M	11	45	Resp	Respiratory failure	same	y
A2171029	1085	3554	73	M	27	59	Neoplasm	Prostate cancer	same	y
A2171029	1088	3616	76	M	17	517	GI	Gastrointestinal bleed, epigastric pain		y
						517	Metab	Hyperglycemia		
A2171029	1093	3854	64	F	10	14	Metab	Hypoglycemia, unconsciousness	same	
					10	21	Metab	Hypoglycemia, unconsciousness	same	
A2171029	1093	3857	62	M	5	316	Metab	Hypoglycemia, loss of consciousness	same; also fall with front teeth injury	
					5	336	Metab	Recurrent hypoglycemia	same	
A2171029	1096	4030	63	M	6	596	Cardiac	Worsening bradycardia		
A2171029	1100	3323	58	M	9	410	GI	Esophageal spasm		

Table 7.1.2.1.3
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = Inhaled Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Patient ID	Age (yrs)	Gender	Dose[1]	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	W/D?[5]
A2171029	1101	4271	60	M	6	168	Cardiac	Congestive heart failure		y
A2171029	1113	5158	68	F	Dose unk	406	Resp	New onset asthma, cough	same	y
A2171029	1115	5408	56	F	8	141	Cardiac	Myocardial infarction		
A2171029	1119	5633	59	F	7	39	Cardiac	Unstable angina		y
A2171029	1119	5661	57	F	7	103	Neoplasm	Cystic nephroma		
A2171030	1015	1393	72	M	12	9	Metab	Ketoacidosis	same	
					12	35	Infec	Pneumonia	same	
A2171030	1018	1691	63	M	24	69	Resp	Recurrence of exacerbation of COPD	same	y
A2171030	1026	2489	68	F	12	191	Resp	COPD exacerbation		
A2171030	1043	4174	64	M	8	85	Accid/ Injur	Accidental fall		
A2171030	1049	5069	75	M	25	26	Accid/ Injur	Fall down stairs, right wrist fracture, fractured ribs		
A2171036	5005	1002	70	M	9	73	GI	Constipation		
						73	Repro/ Uro	Dysuria		
A2171036	5005	1006	70	M	9	97	Cardiac	Myocardial infarction	same	y (death)
A2171036	5007	1006	65	M	8	131	Cardiac	Exacerbation of coronary artery disease		
A2171036	5008	1003	57	M	9	72	Musculoskel	Worsening osteoarthritis knee		
					11	228	Cardiac	Exacerbation coronary artery disease		
A2171036	5010	1004	Unk	M	7	229	Metab	Multinodular goiter		
A2171036	5010	0071	67	M	25	22	Neoplasm	B-cell lymphoma		
A2171036	5011	1004	48	F	18	398	Cardiac	Myocardial infarction	same	y (death)
A2171036	5011	1006	69	M	19	111	Repro/ Uro	Worsening erectile dysfunction		
A2171036	5013	1001	70	F	15	49	Infec	Pyelonephritis		
A2171036	5014	1002	65	M	18	457	Cardiac	Cardiac pacemaker insertion		
A2171036	5014	1006	54	M	7	391	Cardiac	Angina, coronary artery disease		

Includes Studies 1001, 1002, 1005, 1007, 1009, 1017, 1022, 1026, 1027, 1028, 1029, 102E, 103, 1030, 1036, 104, 104E, 106, 107, 108, 109, 110, 111
1 Dose at time of adverse event
2 Duration of exposure in days at time of event. If event occurred after discontinuation, the number of days after discontinuation is included in parentheses
3 Applicant's assigned term
4 Term used by investigator or patient; nb- applicant provided SAE narratives only for pulmonary SAEs and SAEs that led to death or discontinuation
5 If patient withdrew due to this adverse event, noted with a "y"
6 For Study 111, an extension of several clinical trials, it was not clear from the applicant's Table 6.3.1.1 whether a patient had Type 1 or Type 2 diabetes. Readers who wish to examine the

Table 7.1.2.1.3
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = Inhaled Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Patient ID	Age (yrs)	Gender	Dose[1]	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	W/D?[5]
source Table 6.3.1.1 can tell what type of diabetes the patient had by looking at the 5th number of the patient's identification number in the applicant's Table 6.3.1.1. If this number was a zero, 1 or 8, the patient had Type 2 diabetes. If it was any other number, the patient had Type 1 diabetes (telephone communications with Mr Brian Green, Pfizer Regulatory Affairs, 31 Mar 05 and 6 Apr 05)										
Source: Applicant's Table 6.3.1.1, Section 2.7.4, pgs 1903-2296										

Table 7.1.2.1.4
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = SQ Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Pt ID	Age	Gender	Dose[1] (Units), Type SQ Insulin	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
103E	5011	0080	59	F	Isophane 48	413	GI	Cholelithiasis	Mentioned in narrative for pneumonia	
						413	Resp	Pneumonia	same	
						609	GI	Incisional ventral hernia	Mentioned in narrative for pneumonia	
103E	5013	0210	57	F	Isophane 56	54	GI	Fecal impaction		
						54	Urinary	Urinary retention		
108	5007	8056	76	F	Isophane 47, Regular 21	85	Cardiac	Myocardial infarction, coronary artery disease	Mentioned in narrative for abnl end-of-study CXR	
108	5024	8566	60	F	Isophane 104, Regular 47	168	Musculoskel	Back pain		
108	5030	8356	43	M	Isophane 49, Regular 30	46	Metab	Hypoglycemia, possible accidental drug overdose, unconsciousness, motor vehicle accident	same	
108	5037	8465	60	M	Isophane 12, Regular 29	85	Cardiac	Cardiac ischemia	same	y
108	5041	8506	69	M	Isophane 29, Regular 8	73	Accid/ Injur	Motor vehicle accident, broken pelvis, fractured rib	same	y
108	5042	8475	41	M	Isophane 70, Regular 54	63	Infec	Pneumonia, respiratory distress	same	
						63	GI	Ulcerative esophagitis, gastritis, duodenal ulcer	Mentioned in narrative for pneumonia	
						63	Cardiac	Paroxysmal atrial fibrillation	Not mentioned in narrative for	

Table 7.1.2.1.4
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = SQ Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Pt ID	Age	Gender	Dose[1] (Units), Type SQ Insulin	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
									pneumonia	
						63	Heme	Idiopathic anemia	Mentioned in narrative for pneumonia	
108	5048	8428	56	M	Isophane 50, Regular 32	42	Cardiac	Coronary artery block		
108	5049	8378	65	M	Isophane 75, Regular 25	184	Neuro	Stroke		
108	5051	8556	66	F	Isophane 64, Regular 23	140	Neoplasm	Ovarian cancer		
108	5060	8041	67	M	Isophane 54, Regular 24	142	Cardiac	Unstable angina		
						142	Infec	Bilateral pneumonia		
108	5073	8572	60	M	Isophane 100, Regular 37	128	Cardiac	Non-Q wave myocardial infarction		
108	5027	8514	41	F	Isophane 25, Regular 7	89	Skin	Cellulitis		
A2171001	0112	3366	78	F	Isophane 14, Mixtard 52, Metformin 2000, Glibenclamide 7.5	582	Musculoskel	Polymyalgia rheumatica		
					Isophane 64, Mixtard 52, Metformin 2000, Glibenclamide 7.5	596	Metab	Hypoglycemia, syncope		
						596	Musculoskel	Exacerbation of polymyalgia rheumatica		
					Isophane 64, Mixtard 60, Metformin 2000, Glibenclamide 7.5	751	Metab	Hyperglycemia		
A2171027	1002	0050	50	M	Isophane 20, Lispro 3	106	GI	Small bowel obstruction		
						126	GI	Recurrent small bowel obstruction		
						136	GI	Recurrent small bowel obstruction		
A2171027	1008	0351	54	M	Glargine 18, Regular 23	19	Metab	Hypoglycemic episode, loss of consciousness	same	
A2171027	1010	0398	32	M	Glargine 50, Regular 33	56	Accid/ injur	Bone fracture accidental	Fracture of left knee	y
A2171027	1010	0401	39	F	Isophane 48, Regular 23	84	Metab	Hypoglycemia	same	
A2171027	1015	0601	48	M	Isophane 14, Lispro 21	38	Cardiac	Heart attack		
A2171027	1016	0643	30	M	Glargine 32, Lispro 30	25	Metab	Hypoglycemia, loss of consciousness	Hypoglycemia, loss of consciousness, car accident	
A2171027	1019	0790	27	F	Isophane 40, Lispro 18	139	Metab	Hypoglycemia	same	
A2171027	1027	1583	50	M	Isophane 64, Lispro 30	188	Cardiac	Myocardial infarction		
A2171027	5138	1232	61	M	Isophane 16, Lispro 25	30	Metab	Hypoglycemia	same	
					Isophane 16, Lispro 24	135	Metab	Hypoglycemic, coma	Hypoglycemia, not arousable	
A2171028	1051	1280	73	M	Isophane 28, Regular 44	277	Musculoskel	Lumbar vertebrae canal stenosis		
A2171029	1005	0181	65	M	Glargine 20, Lispro 16	Not	Musculoskel	Paracentral disc protrusion		

Table 7.1.2.1.4
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = SQ Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Pt ID	Age	Gender	Dose[1] (Units), Type SQ Insulin	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
						reported (NR)				
						170	Cardiac	Atrial fibrillation		
						172	Cardiac	Atrial fibrillation recurrence		
A2171029	1005	0189	53	F	Glargine 40, Aspart 50	328	Neoplasm	Carcinoid tumor stomach		
A2171029	1006	1608	56	M	Glargine 30, Lispro 34	548	Neuro	Cerebrovascular accident		
A2171029	1007	0242	42	M	Glargine 40, Aspart 40	498	Neuro	Transient ischemic attack		
A2171029	1014	1667	58	M	Glargine 75, Lispro 41	227	Cardiac	Coronary artery disease	Not mentioned in narrative for dyspnea and declines in FEV1, DLco, FVC, TLC	
						227	Resp	Shortness of breath	Dyspnea	
A2171029	1017	0542	67	M	Glargine 14, Lispro 10	4	Infec	Left foot cellulitis, left heel ulceration	same	
					Glargine 20, Lispro 20	150	Metab	Hypoglycemic episode, loss of consciousness	same	
						149	Infec	Osteomyelitis left 3rd toe	same	
A2171029	1019	1727	59	F	Isophane 30, Lispro 12	734	GI	Pancreatitis	same	
A2171029	1020	1788	46	M	Glargine 45, Regular (dose unk)	512	Vasc	Deep vein thrombosis		
A2171029	1022	1847	66	M	Glargine 10, Lispro 19	121	Metab	Hypoglycemic event, unconsciousness	same	
A2171029	1025	1909	57	F	Glargine 35, Aspart 60	59	Metab	Hypoglycemia, panic attack	same	
					Glargine 30, Aspart 45	231	Psych	Bipolar affective disorder aggravated	same	
					Glargine 35, Aspart 63	290	Psych	Bipolar affective disorder aggravated	same	
					Glargine 39, Aspart 86	399	Psych	Relapse of depression	same	
					Glargine 37, Aspart 54	476	Psych	Relapse of depression	same	
A2171029	1033	2144	61	M	Glargine 30, Aspart 27	326	Infec	Pneumonia	same	
A2171029	1039	3022	65	M	Isophane 90, Regular 60	187	Neoplasm	Prostate adenocarcinoma	same	y
A2171029	1044	0959	71	F	Isophane 65, Lispro 15	109	GI	Stomach pain	same	
					Isophane 62, Lispro 14	131	Metab	Hypoglycemic episode	same	
A2171029	1044	0961	51	M	Isophane 108, Regular 72	239	Metab	Hypoglycemia, acute cataplexy, loss of consciousness	same	
A2171029	1044	0965	65	M	Isophane 70, Regular (dose unk)	617	General	Chest pain		

Table 7.1.2.1.4
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = SQ Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Pt ID	Age	Gender	Dose[1] (Units), Type SQ Insulin	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
A2171029	1048	2494	77	F	Glargine 24, Lispro 5	77	Accid/ Injur	Fractured right hip	Not mentioned in narrative for colon cancer	
					Glargine 25, Lispro 15	300	Neoplasm	Colon cancer	same	
					Glargine 15, Lispro 10	380	GI	Vomiting and diarrhea during chemotherapy, weakness	Not mentioned in narrative for colon cancer	
A2171029	1049	2560	58	M	Isophane 60, Regular 20	163	Infect	Cellulitis foot		
						179	Infect	Infected plantar ulcer		
A2171029	1059	2608	37	M	Mixtard (dose unk)	488	Accid/ injur	Motorcycle accident, multiple rib fractures, bilateral pneumothorax	same	
A2171029	1059	2615	44	M	Glargine 41, Lispro 50	207	GI	Partial small bowel obstruction		
					Glargine 40, Lispro 40	365	GI	Obstructed organoaxial volvulus of stomach, recurrent incarcerated incisional hernia, vomiting		
						366	Metab	Hyperglycemia		
A2171029	1064	1080	73	M	Mixtard 59	165	Musculoskel	Progressive left knee pain, osteoarthritis		
A2171029	1065	2794	48	M	Glargine 50, Lispro 23	179	Metab	Hypoglycemia, unconsciousness, seizure	Hypoglycemia, unconsciousness, seizure, tongue laceration	
A2171029	1069	1283	63	F	Isophane 28, Aspart 50	234	Cardiac	Angina pectoris		
A2171029	1074	3142	52	F	Glargine 65, Lispro 30	132	Cardiac	Aortic insufficiency, congestive heart failure, shortness of breath	same	
A2171029	1077	1432	53	F	Glargine 28, Lispro 21	394	Infec	Gastrointestinal infection, vomiting		
A2171029	1078	1491	67	M	Glargine 62, Regular 44	590	Cardiac	Coronary occlusion	Mentioned in narrative for respiratory failure	
							Resp	Hypoxemia	Respiratory failure	
							Renal	Acute renal failure	Mentioned in narrative for respiratory failure	
A2171029	1081	3380	55	F	Glargine 35, Regular 33	79	Metab	Hypoglycemia, loss of consciousness	same	
					Glargine 35, Regular 33	47	Resp	Bronchitis, acute chest pain	Chest pain mentioned in narrative for hypoglycemia	
					Glargine 48, Regular 13	182	Metab	Hypoglycemic episode	Hypoglycemia, jerking movements, unawareness of surroundings	
A2171029	1088	3613	72	M	Mixtard 48	253	Metab	Hypoglycemia	same	
					Mixtard 48	275	Metab	Hypoglycemia	Hypoglycemia, unconsciousness	

Table 7.1.2.1.4
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = SQ Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Pt ID	Age	Gender	Dose[1] (Units), Type SQ Insulin	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
A2171029	1088	3619	69	M	Isophane 12, Regular 25, Lispro 29	575	General	Pain exacerbated		
						575	Neuro	Confusion		
A2171029	1096	4027	61	M	Isophane 27, Regular 35	452	Metab	Hypoglycemia	same	
					Isophane 29, Regular 42	489	Metab	Hypoglycemia	same	
A2171029	1101	4269	49	F	Isophane 46, Lispro 25	189	Neoplasm	Ovarian cancer metastatic		y
A2171029	1110	4977	43	F	Glargine 88, Lispro 45	126	Musculoskel	Multiple sclerosis		
A2171029	1115	5392	55	M	Glargine 70, Regular 18	9	Cardiac	Worsening coronary artery disease		
A2171029	1115	5400	48	F	Isophane 48, Regular 36	464	Psych	Bipolar disorder		
A2171029	1115	5405	56	M	Lispro 31	350	Cardiac	Atrial fibrillation		
A2171029	1118	5583	73	M	Isophane 98, Lispro 37	288	GI	Recurrent inguinal hernia		
						294	Proc Comp	Surgical wound infection		
A2171029	1118	5589	59	F	Isophane 30, Aspart 15	299	Musculoskel	Noncardiac chest muscle pain		
A2171029	1119	5652	76	F	Isophane 68, Regular 18	464	GI	Worsening cholelithiasis		
A2171030	1015	1394	77	M	Mixtard 126	6	Metab	Hypoglycemia, loss of consciousness, hypothermia	same	
						7	GI	Projectile vomiting, nausea		
A2171030	1017	1593	64	M	Isophane 42, Regular 9	329	Repro/ Uro	Bladder neck obstruction		
A2171030	1021	1989	72	M	Isophane 8, Regular 19, Lispro 9	152	GI	Inguinal hernia		
A2171030	1032	3085	64	M	Isophane 49, Regular 19, Metformin 1000, Glipizide 10	93	Cardiac	Myocardial infarction (pt also included in oral agents table)	same	y (death)
A2171030	1043	4176	69	F	Isophane 72, Aspart 54	819	Vasc	Uncontrolled hypertension		
A2171030	1056	5767	75	M	Isophane 57, Regular 60	NR	Cardiac	Myocardial infarction		
A2171030	1078	7941	57	M	Glargine 42, Lispro 48	350	General	Drug maladministration, inadvertently used wrong insulin vial		
A2171030	1078	7944	55	M	Glargine 88, Lispro 66	1221	Cardiac	Exacerbation of coronary artery disease		

Includes Studies 1001, 1002, 1005, 1007, 1009, 1017, 1022, 1026, 1027, 1028, 1029, 102E, 103, 1030, 1036, 104, 104E, 106, 107, 108, 109, 110, 111
1 Dose at time of adverse event
2 Duration of exposure in days at time of event. If event occurred after discontinuation, the number of days after discontinuation is included in parentheses
3 Applicant's assigned term
4 Term used by investigator or patient; nb- applicant provided SAE narratives only for pulmonary SAEs and SAEs that led to death or discontinuation
5 If patient withdrew due to this adverse event, noted with a "y"
Source: Applicant's Table 6.3.1.1, Section 2.7.4, pgs 1903-2296

Table 7.1.2.1.5
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = Oral Agent(s)
Cutoff Date = 1 Sep 04

Trial	Center	Pt ID	Age (yrs)	Gender	Agent/Dose[1] (mg/day)	Time (days)[2]	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
104	5002	0041	42	F	Metformin 1500, Glipizide 10	44	Infec	Boil of labia majora		
104E	5007	0032	60	M	Glipizide 10	55	Neoplasms	Adenocarcinoma prostate	same	y
109	5042	0477	55	F	Pioglitazone 45, Glibenclamide 10	83	Psych	Anxiety	Not mentioned in narrative for decline in DLco with inhaled insulin	
110	5103	1428	63	M	Rosiglitazone 8	37	GI	Gastric ulcer, duodenal ulcer		
110	5123	1069	49	M	Rosiglitazone 8	2	GI	Cholelithiasis		
A2171001	0005	1032	58	M	Metformin 500, Glibenclamide 10	13	Resp	Breathing difficulty		
						13	Cardiac	Ischemic heart disease		
						37	Cardiac	Nonspecific chest pain	Also ischemic heart disease	
A2171001	0027	1066	67	M	Metformin 2000, Glibenclamide 15	99	Cardiac	Inferior myocardial infarction	same	y
A2171001	0035	2333	61	F	Metformin 1500, Glibenclamide 10	189	Musculoskel	Bilateral carpal tunnel syndrome, left carpal tunnel surgery		
A2171001	0035	3021	59	F	Metformin 500, Glibenclamide 5	323	Musculoskel	Hallux valgus		
A2171001	0035	0076	66	F	Metformin 1500, Glibenclamide 15	66	Musculoskel	Acute back pain	same	y
A2171001	0037	1080	71	M	Metformin 2500, Glibenclamide 15	71	Cardiac	Unstable angina pectoris		
A2171001	0045	3361	79	F	Metformin 1500, Glibenclamide 15	202	Metab	Hypoglycemia, unconsciousness	same	
					Metformin 1000, Glibenclamide 15	319	Neoplasm	Ovarian cancer, ascites	same	
A2171001	0046	0099	54	M	Metformin 2000, Glibenclamide 160 (sic)	63	GI	Cholecystitis		
A2171001	0059	1134	35	F	Metformin 500, Glimepiride 4	16	GI	Worsening epigastric pain, vomiting		
A2171001	0085	3005	72	F	Metformin 2000, Glimepiride 3	92	Infec	Skin abscess left hip, infected sebaceous gland scalp		
A2171001	0088	1193	68	M	Metformin 500,	11	Neuro	Cerebrovascular accident	Apoplexy	y

Table 7.1.2.1.5
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = Oral Agent(s)
Cutoff Date = 1 Sep 04

Trial	Center	Pt ID	Age (yrs)	Gender	Agent/Dose[1] (mg/day)	Time (days)[2]	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
					Glimepiride 3					
A2171001	0100	1229	68	F	Metformin 1500, Glibenclamide 15	186	GI	Abdominal pain of unknown origin		
A2171001	0108	1290	71	F	Metformin 1000, Glibenclamide 15	166	Cardiac	Angina pectoris	same	
A2171001	0109	1237	62	M	Metformin 2000, Glibenclamide 15	111	Cardiac	Myocardial infarction	Cardiac infarction	
A2171001	0112	3366	78	F	Metformin 2000, Glibenclamide 7.5	169	Neuro	Syncope	same	
					Metformin 2000, Glibenclamide 7.5, Isophane 14, Mixtard 52	582	Musculoskel	Polymyalgia rheumatica	same	
					Metformin 2000, Glibenclamide 7.5, Isophane 64, Mixtard 52	596	Metab	Hypoglycemia, syncope	same	
					Metformin 2000, Glibenclamide 7.5, Isophane 64, Mixtard 52	596	Musculoskel	Exacerbation of polymyalgia rheumatica	same	
					Metformin 2000, Glibenclamide 7.5, Isophane 64, Mixtard 60	751	Metab	Hyperglycemia	not in narrative	
A2171001	0129	1334	43	M	Metformin 1500, Glimepiride 3	156	Skin	Diabetic ulcer foot	same	y
A2171001	0134	1374	53	M	Metformin 500, Glibenclamide 20	7	Musculoskel	Prolapsed cervical disc	Intervertebral disc disorder	
					Metformin 1000, Glibenclamide 20	215 (31)	Infec	Pneumocystis carinii pneumonia	Pneumonia	
						215 (31)	Resp	Deterioration of lung function	Pneumonia	
A2171001	0138	1280	59	M	Metformin 1500, Glibenclamide 15	252	Vasc	Lower limb arteriopathy worsening		
A2171001	0140	0302	62	M	Metformin 2000, Glibenclamide 15	260	Accid/ Injur	Broken ribs	same	
A2171001	0140	1302	61	F	Metformin 1500, Glibenclamide 17.5	182 (17)	GI	Gastroesophageal pyrosis, esophageal spasm	Narrative reports diarrhea	
A2171001	0141	2068	84	M	Metformin 1500, Glibenclamide 10	684	Neoplasm	Basal cell carcinoma skin		

Table 7.1.2.1.5
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = Oral Agent(s)
Cutoff Date = 1 Sep 04

Trial	Center	Pt ID	Age (yrs)	Gender	Agent/Dose[1] (mg/day)	Time (days)[2]	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
A2171001	0142	3057	67	M	Metformin 2000, Glibenclamide 20	196	Musculoskel	Multiple fractures		
A2171002	0002	7338	57	M	Metformin 2000, Glibenclamide 2.5	698	Repro/ Uro	Transurethral resection of prostate		
A2171002	0004	8010	64	F	Metformin 2500, Glibenclamide 12.5	?	GI	Epigastric hernia	Not in narrative	
					Metformin 2500, Glibenclamide 12.5	242	General	Chest pain	same	
A2171002	0005	5030	64	M	Metformin 2000, Glibenclamide 2.5	57	Cardiac	Persistent atrial flutter	same	
					Metformin 2000, Glibenclamide 2.5	89	Accid/ Injur	Car accident	same	y (death)
A2171002	0005	6029	50	F	Metformin 2000, Glibenclamide 7.5	84	GI	Acute pancreatitis		
A2171002	0005	6030	54	F	Metformin 1000, Glibenclamide 2.5	118	GI	Unspecified upper abdominal pain		
A2171002	0027	7365	58	F	Metformin 2000, Glibenclamide 15	213	Infec	Urosepsis		
A2171002	0029	5054	51	M	Metformin 2000, Glibenclamide 7.5	339	Cardiac	Heart attack	Acute anterior myocardial infarction	y
A2171002	0035	6057	54	F	Metformin 2000, Glibenclamide 7.5	48	Musculoskel	Bilateral carpal tunnel syndrome		
A2171002	0035	7330	52	F	Metformin 2000, Glibenclamide 7.5	210	GI	Food poisoning		
A2171002	0038	8025	66	M	Metformin 2000, Glibenclamide 7.5	680	Cardiac	Acute anteroseptal myocardial infarction		
A2171002	0045	5077	74	F	Metformin 1500, Glibenclamide 2.5	8 (100)	Cardiac	Myocardial infarction	same	Prev dc; death from this SAE
A2171002	0047	6086	59	M	Metformin 2000, Glibenclamide 10	83	Cardiac	Acute myocardial infarction	same	y (death)
A2171002	0047	7342	69	F	Metformin 2000, Glibenclamide 10	608	Repro/ Uro	Prolapsed uterus		
A2171002	0047	8322	67	M	Metformin 2000, Glibenclamide 10	106	GI	Acute cholecystitis, esophagitis	Same terms included in narrative for lung fibrosis on CXR	
A2171002	0049	5089	53	M	Metformin 2000,	230	Eye	Eye movement disorder	Strabismus mentioned in	

Table 7.1.2.1.5
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = Oral Agent(s)
Cutoff Date = 1 Sep 04

Trial	Center	Pt ID	Age (yrs)	Gender	Agent/Dose[1] (mg/day)	Time (days)[2]	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
					Glibenclamide 7.5				narrative for decline in FEV1	
A2171002	0051	5093	63	M	Metformin 2000, Glibenclamide 7.5	369	Neuro	Vestibular neuritis		
A2171002	0051	6096	59	M	Metformin 2000, Glibenclamide 10	121	Musculoskel	Hammer toe		
A2171002	0056	8050	61	M	Metformin 2000, Glibenclamide 5	295	Eye	Ischemic optic neuropathy		
						?	Musculoskel	Right sided coxarthrosis		
						145	Neuro	Peripheral paresis of right facial nerve		
A2171002	0058	6117	53	F	Metformin 2000, Glibenclamide 7.5	54	GI	Abdominal discomfort		
A2171002	0073	6145	46	M	Metformin 2000, Glibenclamide 10	57	Cardiac	Congestive heart failure	same	y
A2171002	0074	5151	54	M	Metformin 2000, Glibenclamide 2.5	613	Resp	Dyspnea	Same term mentioned in narrative for abnormal CXR	
						632	Repro/ Uro	Renal calculus	Kidney pain mentioned in narrative for abnormal CXR	
A2171002	0074	5152	73	M	Metformin 1000, Glibenclamide 2.5	730	Vasc	Narrowing left renal artery		
					Metformin 2000, Glibenclamide 2.5	14	Vasc	Worsening right inferior limb arteritis		
A2171002	0083	5165	58	F	Metformin 2000, Glibenclamide 2.5	63	Neoplasm	Small cell bronchus carcinoma	Bronchial carcinoma	y
A2171002	0085	5169	74	F	Metformin 2000, Glibenclamide 10	124	Musculoskel	Lumbalgia		
A2171002	0092	5189	59	M	Metformin 2000, Glibenclamide 10	138	Vasc	Stenosis carotid artery		
A2171002	0096	5202	48	M	Metformin 2000, Glibenclamide 5	165	Musculoskel	Pectoralis muscle inflammation		
A2171002	0096	5203	62	M	Metformin 2500, Glibenclamide 5	58	Cardiac	Cardiac infarction	Heart infarction	y (death)
A2171002	0141	8027	69	F	Metformin 2000, Glibenclamide 7.5	26	Neuro	Hydrocephalus acquired worsening		
					Metformin 2000, Glibenclamide 10	335	Neuro	Hydrocephalus acquired worsening		
A2171002	0141	8032	62	M	Metformin 2000, Glibenclamide 10	533	Cardiac	Cardiac arrhythmia, angina		

Table 7.1.2.1.5
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Adult Type 2 Diabetics
Sorting by Patient
Treatment = Oral Agent(s)
Cutoff Date = 1 Sep 04

Trial	Center	Pt ID	Age (yrs)	Gender	Agent/Dose[1] (mg/day)	Time (days)[2]	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
A2171002	0141	8037	49	F	Metformin 2000, Glibenclamide 10	454	Repro/ Uro	Dysfunctional uterine hemorrhage		
A2171002	0142	7041	65	M	Metformin 2000, Glibenclamide 10	220	Cardiac	Worsening of angina		
A2171002	0142	7406	46	M	Metformin 2000, Glibenclamide 5	188	Neoplasm	Colon adenocarcinoma		
						258	GI	Biliary colic		
A2171002	0142	7409	53	M	Metformin 2000, Glibenclamide 2.5	5	Vasc	Intermittent claudication worsening		
					Metformin 2000, Glibenclamide 12.5	321	Infec	Suture line abscess right leg		
A2171002	0142	8379	56	F	Metformin 2000, Glibenclamide 10	98	Repro/ Uro	Renal lithiasis		
A2171017	1003	1002	70	M	Glipizide 10, Metformin 2000, Rosiglitazone 8	209	Cardiac	Recurrent angina		
A2171017	1036	1002	55	M	Rosiglitazone 8, Metformin 2000, Glimepiride 7.5	218	Neuro	Subarachnoid hemorrhage		
A2171017	1037	1002	51	M	Glipizide 20, Metformin 2000, Rosiglitazone 4	68	Cardiac	Angina		
A2171030	1032	3085	64	M	Metformin 1000, Glipizide 10, Isophane 49, Regular 19	93	Cardiac	Myocardial infarction (event also in SQ table)		

Includes Studies 1001, 1002, 1005, 1007, 1009, 1017, 1022, 1026, 1027, 1028, 1029, 102E, 103, 1030, 1036, 104, 104E, 106, 107, 108, 109, 110, 111
1 Dose at time of adverse event
2 Duration of exposure in days at time of event. If event occurred after discontinuation, the number of days after discontinuation is included in parentheses
3 Applicant's assigned term
4 Term used by investigator or patient; nb- applicant provided SAE narratives only for pulmonary SAEs and SAEs that led to death or discontinuation
5 If patient withdrew due to this adverse event, noted with a "y"
Source: Applicant's Table 6.3.1.1, Section 2.7.4, pgs 1903-2296

Table 7.1.2.1.6
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Pediatric Patients
Sorting by Patient
Treatment = Inhaled Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Pt ID	Age (yrs)	Gender	Dose[1] (mg)	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
106	5082	6093	14	F	8	165	Metab	Diabetic ketoacidosis		
107	5083	7499	17	M	6	8	Metab	Hypoglycemia, dehydration		
						8	GI	Emesis		
107	5084	7336	13	M	18	133	Musculoskel	Fracture tibia and fibula		
107	5090	7455	13	M	4	133	Metab	Hypoglycemia	Mentioned in narrative for decline in TLC	
						133	GI	Nausea, vomiting	Mentioned in narrative for decline in TLC	
111	5064	6103	16	M	20	622	Metab	Diabetic ketoacidosis	same	y
111	5064	6105	15	F	17	20	Metab	Diabetic ketoacidosis		
					18	604 (40)	Metab	Recurrent diabetic ketoacidosis		
111	5064	6517	13	F	10	46	Metab	Diabetic ketoacidosis		
111	5064	6519	16	F	18	308	GI	Pancreatitis	same	y
					18	308	Metab	Diabetic ketoacidosis	same	
111	5064	6524	13	M	16	66	Metab	Ketoacidosis	Not mentioned in narrative for later episode of DKA	
					30	294	Metab	Diabetic ketoacidosis	same	y
111	5078	7408	15	M	14	925	Metab	Diabetic ketoacidosis		
111	5079	3322	11	F	25	371	Infec	Nausea, vomiting, viral gastroenteritis		
111	5079	3324	12	F	12	605 (26)	Metab	Diabetic ketoacidosis	Mentioned in narrative for high Ab titre	
111	5082	3341	11	F	22	832	Metab	Hypoglycemia, seizure	same	
111	5082	3346	10	M	24	657	Metab	Hypoglycemia	same	
111	5082	3347	8	M	13	346	Metab	Hypoglycemia, seizure	same	
111	5082	3348	8	M	24	126	Neuro	Headaches	Mentioned in narrative for hypoglycemic events	
					45	310	Metab	Hypoglycemia, mental status change left-sided weakness	same	
					42	446	Metab	Hypoglycemia	hypoglycemia, unresponsiveness	
					33	565	Infec	Gastroenteritis, dehydration	Not mentioned in narrative for hypoglycemic events	
					42	578	Metab	Hypoglycemia, possible seizure	same	
111	5082	6090	13	M	12	351	Resp	Right pleural effusion	persistent/ recurrent pleural effusion, pleuroperitoneal shunt placement	y
111	5082	6091	12	F	14	129	Infec	Gastroenteritis, dehydration		
111	5082	6493	16	M	20	384	Accid/ Injur	Headache, nausea, sports injury		
111	5084	3037	10	F	2	193	Accid/ Injur	Accidental fall, fractured femur		

Table 7.1.2.1.6
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Pediatric Patients
Sorting by Patient
Treatment = Inhaled Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Pt ID	Age (yrs)	Gender	Dose[1] (mg)	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
111	5084	7002	16	F	18	799	Metab	Diabetic ketoacidosis		
111	5086	7533	15	M	24	266	Accid/ Injur	Fracture left wrist		
111	5087	7011	17	M	27	1156	Metab	Hypoglycemic episode	same	
111	5088	3384	7	F	5	191	Metab	Hypoglycemia, seizure, accidental drug overdose of inhaled insulin	same	
111	5089	3025	11	F	11	67	Metab	Diabetic ketoacidosis	same	y
111	5091	3008	13	M	28	708 (156)	Metab	Diabetic ketoacidosis	Not mentioned in narrative for hypoglycemia	
					29	708 (176)	Metab	Diabetic ketoacidosis	Not mentioned in narrative for hypoglycemia	
					16	141	Metab	Hypoglycemia, seizure	same	
					20	452	Metab	Diabetic ketoacidosis	Not mentioned in narrative for hypoglycemia	
111	5091	3373	11	M	14	364	Metab	Accidental overdose Lantus insulin		
111	5091	3373	12	M	17	575	GI	Nausea, vomiting, food poisoning		
111	5091	3374	12	M	15	418	Infec	Viral syndrome		
					15	418	Metab	Diabetic ketoacidosis		
111	5091	6074	16	F	10	796	Metab	Diabetic ketoacidosis		
					13	19	Metab	Ketonuria		
					13	19	GI	Vomiting		
111	5091	6076	15	M	18	80	Metab	Diabetic ketoacidosis		
					18	80	Infec	Vomiting, viral syndrome, gastroenteritis		
111	5091	6474	13	F	18	85	Metab	Diabetic ketoacidosis		
111	5091	6475	16	M	9	91	Metab	Diabetic ketoacidosis		
					9	91	Infec	Viral syndrome		
111	5092	6487	16	M	12	751	Accid/ Injur	Bicycle accident		
111	5093	7039	16	F	13	986 (13)	Metab	Diabetic ketoacidosis		
111	5093	7040	14	M	14	394	Infec	Nausea, vomiting		
111	5093	7392	16	F	7	269	Psych	Suicidal tendencies		
					7	346	Psych	Suicidal tendencies, intentional overdose alcohol and acetaminophen		
111	5094	7094	14	M	13	277	Infec	Stomach flu	Not mentioned in narrative for hypoglycemia	
					14	599	Metab	Hypoglycemia	same	
111	5095	3334	7	M	8	240	Metab	Hypoglycemia	same	

Table 7.1.2.1.6
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Pediatric Patients
Sorting by Patient
Treatment = Inhaled Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Pt ID	Age (yrs)	Gender	Dose[1] (mg)	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
111	5096	3358	12	M	21	585	Metab	Hypoglycemia, partial seizure	same	
111	5096	3359	10	M	8	435	Metab	Hypoglycemia, seizure	same	
111	5098	3048	10	M	6	569	Metab	Hypoglycemia, seizures		
					9	380	Metab	Hypoglycemia, seizure	same	
111	5108	7077	16	F	23	825 (21)	Psych	Exacerbation of depression		
					24	825 (21)	Metab	Diabetic ketoacidosis		
					26	825 (102)	Psych	Depressive disorder		
					25	691	Psych	Depressive disorder		
A2171009	5088	3381	7	F	8	78	Metab	Hypoglycemia, unresponsiveness		
A2171009	5095	3339	11	M	20	49	Psych	Suicidal ideation		
A2171009	5096	3021	10	F	19	46	Metab	Hypoglycemic event, possible seizures		

1 Dose at time of adverse event
2 Duration of exposure in days at time of event. If event occurred after discontinuation, the number of days after discontinuation is included in parentheses
3 Applicant's assigned term
4 Term used by investigator or patient; nb- applicant provided SAE narratives only for pulmonary SAEs and SAEs that led to death or discontinuation
5 If patient withdrew due to this adverse event, noted with a "y"
Source: Applicant's Table 6.3.1.1, Section 2.7.4, pgs 1903-2296

Table 7.1.2.1.7
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Pediatric Patients
Sorting by Patient
Treatment = SQ Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Pt ID	Age (yrs)	Gender	Dose[1] (U/day)	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
107	5063	7419	17	F	Isophane 84, Regular 82	156	Metab	Diabetic ketoacidosis		
107	5079	7479	16	M	Isophane 65, Regular 74	91	Metab	Diabetic ketoacidosis		
						91	GI	Hematemesis		
107	5098	7073	13	F	Isophane 80, Regular 20	201	Metab	Severe hypoglycemic event, seizures	same	
A2171009	5082	3347	7	M	Zinc suspension 22, Regular 20	36	Metab	Hypoglycemic, seizure	same	

Table 7.1.2.1.7
Serious Adverse Event Listing
All Clinical Pharmacology, Phase 2 and Phase 3 Clinical Trials in Pediatric Patients
Sorting by Patient
Treatment = SQ Insulin
Cutoff Date = 1 Sep 04

Trial	Center	Pt ID	Age (yrs)	Gender	Dose[1] (U/day)	Time[2] (days)	Body System	Applicant's Assigned Term[3]	Investigator's Term (if different)[4]	D/C?[5]
A2171009	5096	3022	11	M	Isophane 28, Regular 8	92	Infec	Herpes zoster		

1 Dose at time of adverse event
2 Duration of exposure in days at time of event. If event occurred after discontinuation, the number of days after discontinuation is included in parentheses
3 Applicant's assigned term
4 Term used by investigator or patient; nb- applicant provided SAE narratives only for pulmonary SAEs and SAEs that led to death or discontinuation
5 If patient withdrew due to this adverse event, noted with a "y"
Source: Applicant's Table 6.3.1.1, Section 2.7.4, pgs 1903-2296

Table 7.1.2.1.8
Serious Adverse Event Listing
Nondiabetic Subjects
Sorting by Patient
All Treatments
Cutoff Date = 1 Sep 04

Trial	Center	Pt ID	Age	Gender	Dose[1]	Time[2] (days)	Body System	Preferred Term[3]	Investigator AE Term[4]	D/C?[5]
A2171005	5139	0076	71 yrs	M	Crossover inhaled and SQ; last treatment SQ 9 U	Single dose Study Day 19, after 8 day washout, ACS Study Day 21, MI Study Day 23	Cardiac	Acute myocardial infarction, hypotension	same	
A2171005	5139	0085	67 yrs	M	Crossover inhaled and SQ; last treatment inhaled insulin 3 mg	Single dose Study Day 13, after 3 day washout; event Study Day 13	Cardiac	Myocardial infarction	same	
A2171022	1039	Nonsubject 01	1 day	M	Inhaled insulin 7 (to mother)	From conception through appr 25 days in utero	General	Drug exposure in utero		y (death)
							Cardiac	Cardiomegaly, congestive heart failure, cardiogenic shock		
							Metab	Fetal macrosomia		

Includes Studies 1001, 1002, 1005, 1007, 1009, 1017, 1022, 1026, 1027, 1028, 1029, 102E, 103, 1030, 1036, 104, 104E, 106, 107, 108, 109, 110, 111
1 Dose at time of adverse event
2 Duration of exposure in days at time of event. If event occurred after discontinuation, the number of days after discontinuation is included in parentheses
3 Applicant's assigned term
4 Term used by investigator or patient
5 If patient withdrew due to this adverse event, noted with a "y"
Source: Applicant's Table 6.3.1.1, Section 2.7.4, pgs 1903-2296

10.5 Serious Adverse Event Narratives

These narratives relate to Section 7.1.2 of the main body of the review. Patients are identified by their study number, then their center number, then their patient ID number.

Serious Accidents and Injuries

A2171002-0002-7337: 69 yo man with Type 2 DM, treated with inhaled insulin and metformin. On day 673 of inhaled insulin treatment, fell while using a mall escalator and experienced head trauma with loss of consciousness lasting a few seconds. Hospitalized on neurosurgery ward for two weeks, then transferred to rehabilitation. Applicant states no history of hypoglycemia prior to the fall. No blood glucose values in narrative. Inhaled insulin permanently discontinued on day of fall.

A2171022-1006-0302: 37 yo man with Type 1 DM, treated with inhaled insulin and subcutaneous isophane insulin. On Day 31 of inhaled insulin, patient had a motorcycle accident; did not have recorded hypoglycemia prior to the accident. In the emergency room, had psychomotor agitation and was given 40 mL of 50% glucose. BG prior to administration of glucose not in narrative, but narrative states that patient recovered from hypoglycemia that evening. Had left clavicular rhegma which required shoulder immobilization; was discharged later that night. On day 192 of inhaled insulin, patient had a hypoglycemic episode with a blood glucose of 27 mg/dL at 1846. At 2030, was taken to the ER, where he had a BG of 34 mg/dL. Received 500 cc 10% dextrose in ER; within 30 minutes, BG was 142. Discharged to home that evening.

103E-5005-0063: 58 yo woman with Type 2 diabetes, treated with inhaled insulin and zinc suspension insulin. On day 180 of inhaled insulin treatment, patient had a "moderate" episode of syncope while driving, and had an MVA. Specific injuries not mentioned. Blood sugar status not mentioned. While in the ER after the MVA, pneumonia noted. Treated with clindamycin. Hospitalized for 17 days.

Serious Cardiac Adverse Events

A2171001-0093-1209: 64 yo man with Type 2 DM, treated with inhaled insulin. Episodes of angina on inhaled insulin days 56 and 94. On day 109, dyspnea, burning chest pain, vertigo. Left anterior descending coronary artery (LAD) stenosis noted; successful percutaneous transluminal coronary angioplasty (PTCA) study day 116. At end of trial, also had decline in FEV1 (3.76-3.09 L) and DLco (30.9-22.7 mL/min/mmHg).

A2171005-5139-0076: 71 yo nondiabetic man with chronic bronchitis enrolled in PK study with salbutamol coadministration. Received a single dose of inhaled insulin on Study Days 1 and 6, both followed by salbutamol. On Study Day 19, received a single injection of 9 u regular insulin SQ, preceded by salbutamol. On Study Day 21, experienced diaphoresis and chest pressure; cardiac enzymes negative. On Study Day 23, had myocardial infarction with CABG that same day; experienced postoperative hypotension. Discharged on Study Day 31.

A2171005-5139-0085: 67 yo nondiabetic man with chronic bronchitis enrolled in PK study with salbutamol coadministration. Received a single dose of inhaled insulin on Study Days 1 and 13, and a single dose of SQ insulin on Study Day 9. On Study Day 13, after inhaled insulin administration, became diaphoretic after a large meal. Went to ER and was diagnosed with an MI with elevated enzymes. Catheterization revealed diffuse minimal irregularities, with a circumflex coronary vessel thrombus. Treated with coumadin. Discharged on Study Day 20.

103E-5002-0010: 39 yo man with Type 2 DM treated with inhaled insulin and zinc suspension insulin. Narrative states that on day 1110, coronary arteriosclerosis was reported, but precise event not described. Patient had previously undergone pulmonary consultation for cough, wheezing and decline in lung diffusion capacity for carbon monoxide (DLco). On Study Day 1110, experienced "ongoing moderate coronary artery disorder". Was discontinued from study on Day 1172 due to coronary artery disorder.

111-5034-8035: 66 yo man with Type 2 DM, treated with inhaled insulin and NPH. On day 727, while recovering from a cystourethroscopy, pt experienced a severe myocardial infarction. Four days later, he underwent CABG; discharged to home 5 days after CABG.

111-5049-8378: 67 yo man with Type 2 DM, treated with inhaled insulin. Inhaled insulin was discontinued on day 637 in preparation for CABG, which was performed 5 days later. Narrative states that "event of worsening coronary artery disease was considered resolved" 8 days post-CABG.

111-5055-0581: 70 yo man with Type 2 DM, treated with inhaled insulin and metformin. On day 717 of inhaled insulin treatment, patient was diagnosed with severe congestive heart failure with severe global hypokinesia, EF of 33%, large apical thrombus, enlarged left atrium. Two months later, ECG showed inferior MI. Narrative states that eight months after CHF diagnosed, was considered resolved. Patient also had decline in FEV1, FVC, and TLC.

111-5060-0664: 56 yo man with Type 2 DM, treated with inhaled insulin, metformin and glyburide. On day 132 of inhaled insulin treatment (84 in Study 109 and 48 in Study 111), patient was admitted to hospital with chest pain and diagnosed by ECG with acute MI. Inhaled insulin was discontinued temporarily. Underwent CABG and was discharged 6 days after MI. Pt had another MI 44 days later and was permanently discontinued from study.

111-5060-0672: see Serious Neoplastic Events

111-5060-8110: 53 yo man with Type 2 DM, treated with inhaled insulin and UL. On day 562 of inhaled insulin administration, patient presented with new onset unstable angina and borderline elevations in cardiac enzymes. Inhaled insulin was discontinued on admission. Three days later, cardiac catheterization revealed severe proximal LAD occlusion with a possible dissection of the LAD. Pt underwent CABG that day. He was discharged to home 5 days later.

111-5062-0642: 49 yo man with Type 2 DM, treated with inhaled insulin monotherapy. Patient began study with abnormal PFTs (mild peripheral airways obstruction). On day 113 of inhaled

insulin administration, patient experienced dyspnea on exertion. On day 181 of inhaled insulin administration, PFTs showed a significant decline in DLco from baseline. Inhaled insulin was discontinued after 282 days of administration. Twenty-two days after discontinuation of inhaled insulin, coronary angiography revealed occlusion of the high first diagonal branch, an 80% mid-circumflex lesion, and a complex 90% stenosis of the right coronary artery. PTCA dilated the right coronary and circumflex arteries; shortness of breath improved. PFTs done 24 days after PTCA revealed improvements in FVC and FEV1, but DLco is not mentioned.

111-5076-0700: 65 yo man with Type 2 DM, treated with inhaled insulin, glyburide and metformin. On day 335 of inhaled insulin administration, patient awoke with left arm pain, which did not respond to sublingual nitroglycerin. The next morning, he awoke with similar pain and presented to the ER. He was admitted with a diagnosis of myocardial infarction, with a peak serum creatine phosphokinase (CPK) of 448 U/L. ECG showed inferior ischemic changes; echocardiogram showed "minimal" left ventricular dysfunction, EF 50-59%, moderated aortic stenosis (AoS). He was treated with heparin, integrilin and oxygen. Inhaled insulin was discontinued and never restarted. Seven days after admission, he underwent 4-vessel CABG and aortic valve replacement (AoVR).

Serious Gastrointestinal Adverse Events

A2171002-0142-8380: 70 yo man with Type 2 DM, treated with inhaled insulin and metformin. On day 25 of inhaled insulin, developed severe acute biliary pancreatitis, which resolved on Study Day 50. Investigator felt event due to biliary lithiasis. At time of event, alanine aminotransferase (ALT), total bilirubin (bili), gamma-glutamyl transferase (GGT) and alkaline phosphatase (alk phos) were within normal limits (wnl). Patient permanently discontinued on Study Day 57 due to this event.

A2171022-1010-0537: 48 yo man with Type 1 DM, treated with inhaled insulin and subcutaneous insulin glargine. On day 314 of inhaled insulin, admitted to hospital with nausea, vomiting and hypoglycemia. Diagnosed with gastroenteritis. Inhaled insulin temporarily discontinued while patient in hospital. Hospitalized for four days; discharged and readmitted one day later for recurrent nausea, vomiting and hypoglycemia. Gastroenteritis resolved 4 days later. Patient also had developed high titers of anti-insulin antibodies.

111-5064-6519: 16 yo girl with Type 1 DM, treated with inhaled insulin and UL. On day 308 of inhaled insulin administration, the patient was admitted to the hospital with severe abdominal pain, nausea and vomiting. She was diagnosed with pancreatitis and diabetic ketoacidosis. Amylase was 309 U/L (nl range for lab not reported; std ref range 60-180 U/L, Harrison's 16th Ed) and lipase was 839 U/L (std ref range 0-160 U/L, Harrison's 16th Ed). Serum glucose was 247 mg/dL, beta-hydroxybutyrate was 3.5 mmol/L (uln 3.0), and serum bicarbonate was 12 mmol/L. Inhaled insulin was permanently discontinued on admission by the primary investigator due to "lack of efficacy". Abdominal ultrasound was normal; etiology of pancreatitis not determined. Patient was discharged 7 days after admission.

Serious Metabolic Adverse Events

A2171009-5088-3381: 8 yo girl with Type 1 DM, treated with inhaled insulin and subcutaneous isophane insulin. On Day 78 of inhaled insulin administration, after lunch, went to school nurse complaining that she didn't feel well; became unresponsive and fell to the floor. Fingerstick glucose 28 mg/dL. Paramedics administered IV glucose en route to ER. Patient had had several low blood sugars during the week prior to the event. Discontinued from study on Day 78.

A2171009-5096-3021: 10 yo girl with Type 1 DM, treated with inhaled insulin and subcutaneous isophane insulin. On Day 46 of inhaled insulin, patient awoke her mother at 0429; patient appeared confused and lethargic. BG 50; given half can of cola. At 0443, BG 346, but still confused and lethargic. At 0455, BG 72. Mother called doctor, who told mother to give 1 mg glucagon. At 0552, patient still confused and lethargic. Mother drove child to ER; child vomited en route. Head CT negative; BG 128 mg/dL. Admitted to neurology ward; felt to possibly have had seizures; recovered and was discharged the following day.

A2171022-1001-0009: 37 yo man with Type 1 DM, treated with inhaled insulin and subcutaneous isophane insulin. On Day 197 of inhaled insulin, was found unconscious in the early morning hours by his wife. She called paramedics, who administered IV glucose. BG by paramedics was 1.1 mmol/L (20 mg/dL) at 0445. Regained consciousness and was stable within one hour of receiving IV glucose. The previous evening at 1930, pt had had BG of 1.8 mmol/L (33 mg/dL), which he had self-treated. BG at 0130 had been 12.7 mmol/L (231 mg/dL); nighttime isophane dose 10 units. Discontinued inhaled insulin on Study Day 202.

A2171022-1015-0837: 37 yo man with Type 1 DM, treated with inhaled insulin and subcutaneous insulin glargine. On day 82 of inhaled insulin administration, had a "moderate" hypoglycemic event with a BG of 38 mg/dL, which resolved after eating breakfast. On day 84 of inhaled insulin administration, at 0430, patient had hypoglycemia and loss of consciousness. EMS measured BG at 35 mg/dL; transported to hospital. Narrative states that patient had administered supper insulin based on his post-supper value, rather than on his pre-supper value.

A2171022-1025-1424: 32 yo man with Type 1 DM, treated with inhaled insulin and subcutaneous insulin glargine. In the early morning of day 244 of inhaled insulin administration, had a headache accompanied by confusion and a change in affect. Patient felt hypoglycemic and ate 15-20 gms of carbohydrate at 0630 without checking BG; BG at 0730 after food was 99 mg/dL. Mental status changes persisted and patient was admitted to the hospital for hypoglycemia and seizure; details of seizure activity not provided. Hypoglycemia and seizure resolved that day. EEG on Study Day 245 showed excessive "low" wave discharges in the left hemisphere, particularly in the temporal lobe, interpreted as c/w underlying focal cerebral dysfunction. CT of head on Study Day 246 was "benign". MRI head normal (nl) on Study Day 248.

A2171022-1026-1489: 22 yo man with Type 1 DM, treated with inhaled insulin and subcutaneous isophane insulin. On Study Day 482, while driving to work and before eating breakfast, patient became hypoglycemic and had a motor vehicle accident "when he was unable to stop his vehicle". He was disoriented after the accident and was transported to the hospital by

paramedics and treated with intravenous glucose. He did not have injuries and was released from the emergency room later that day.

A2171022-1029-1661: 35 yo man with Type 1 DM, treated with inhaled insulin and SQ insulin glargine. On day 89 of inhaled insulin treatment, wife was unable to arouse the patient; she called an ambulance; when they arrived, BG was 49 mg/dL and pt was treated with IV glucose. Pt recovered and was not transported to the hospital.

A2171022-1037-2136: 52 yo woman with Type 1 DM, treated with inhaled insulin and SQ isophane insulin. On day 14 of inhaled insulin administration, patient manifested confusion, "irrational behavior", and loss of consciousness. A neighbor called EMS; pt initially refused transport to the hospital, but paramedics measured BG at 20 mg/dL at 0630 and pt transported to hospital per paramedic protocol. Paramedics noted marked tremulousness with exaggerated tremors of both upper extremities, but did not note frank seizure activity. In ER at 0815, BG was 51 mg/dL, blood alcohol was 0.07% (legal limit 0.8%). Hypoglycemia and mental status changes resolved that day. The day prior, patient had had erratic food and insulin intake. In response to this event, doses of inhaled and isophane insulin were halved.

A2171022-1050-3914: 46 yo man with Type 1 DM, treated with inhaled insulin and SQ isophane. Had three serious hypoglycemic episodes over the course of his participation in study, on Study Days 3, 162 and 165. On Study Day 3, had a presupper (1800) BG of 47 mg/dL; ate supper with protein and multiple carbohydrates (carbs). At 1930 became confused and disoriented; BG 35. Treated with soda and glucose tablets, with resolution. On Study Day 162 at 0630, was incoherent and unable to treat himself. Ambulance called and patient treated by EMS; was not transported to the hospital. A nearly identical event occurred on Study Day 165.

A2171022-5074-3082: 51 yo woman with Type 1 DM, treated with inhaled insulin and isophane insulin. On day 167 of inhaled insulin administration, had "hypoglycemic symptoms" at 0230 and was brought to the emergency room. She recovered and was discharged from the ER after "a few hours". Patient also had insulin antibodies >2,000 μU/mL by Esoterix® assay.

A2171022-5147-3376: 45 yo female with Type 1 DM, treated with inhaled insulin and crystalline zinc suspension insulin. Each day on days 89, 92 and 93 of inhaled insulin administration, patient became disoriented between 0530 and 0630, and later found herself "coming to" in another room, or doing something of which she had no recollection. Blood sugars after "coming to" were 38 mg/dL and 33 mg/dL for the episodes on days 89 and 92 respectively. She self-treated with carbohydrate for each of these episodes, and did not seek medical attention at the time, but reported the episodes at her next study visit.

A2171026-1001-0017: 50 yo female with Type 1 DM, treated with inhaled insulin, isophane insulin and regular insulin. On the morning of day 10 of inhaled insulin treatment, patient's husband found her semiconscious and unresponsive. Husband administered glucagon and patient recovered that day. Blood sugar at 0420 that day was 31 mg/dL; narrative does not state whether this was a blood sugar from the time of the hypoglycemic episode.

A2171027-5148-1329: 43 yo man with Type 1 DM, treated with inhaled insulin and isophane insulin. On day 4 of inhaled insulin, consumed a 20 oz beer at a hockey game at 2000. At 2105, became dizzy, sweaty, confused and began to mumble; he then lost consciousness for 25 minutes. EMS called; on their arrival, BG 18 mg/dL. EMS treated pt with IV glucose; pt recovered and was not hospitalized.

A2171029-1059-2607: 45 yo man with Type 2 DM, treated with inhaled insulin and insulin glargine. On day 223 of inhaled insulin treatment, while patient was undergoing a gallium scan as part of a pulmonary evaluation, patient began twitching and had a BG of 25 mg/dL, followed by a seizure. Time of day of event not mentioned, but occurred after breakfast. He was treated with glucose and hospitalized; discharged later that day with a reduction in inhaled insulin dose.

A2171029-1093-3854: 64 yo woman with Type 2 DM treated with inhaled insulin and isophane. On day 14 of inhaled insulin, patient had no oral intake except some juice at 1200. At 2200, pt's daughter found pt unconscious; daughter called EMS. BG by EMS 38 mg/dL; EMS gave IV glucose and transported patient to hospital. Discharged early the next morning. On day 22 of inhaled insulin, after a day of relatively good oral intake, pt became unconscious at night and EMS was called. BG by EMS at 2122 was 35 mg/dL. EMS gave IV glucose; pt recovered and was not taken to hospital. Inhaled insulin dose decreased.

A2171029-1093-3857: 62 yo man with Type 2 DM treated with inhaled insulin and isophane. On day 316 of inhaled insulin treatment, patient lost consciousness sometime after lunch, and remained unconscious for approximately 7 hours. When patient lost consciousness, he fell and injured his front teeth. Prelunch BG had been 78 mg/dL. After recovering consciousness, patient ate carbohydrate; he did not go to hospital, but saw his primary care physician the next day. On day 336 of inhaled insulin treatment, patient lost consciousness from 1400 and 1600. Pt had not had lunch. EMS was called; BG at 1500 was 31 mg/dL. Treated with IV glucose; no report of transfer to hospital.

A2171030-1015-1393: 72 yo man with Type 2 DM treated with inhaled insulin and isophane. On day 9 of inhaled insulin treatment, after eating at a restaurant, developed nausea and vomiting. Did not take evening insulin for fear of becoming hypoglycemic. Admitted that night with DKA. Reportedly treated with regular SQ insulin sliding scale; DKA resolved 2 days later.

106-5025-6592: 36 yo man with Type 1 DM, treated with inhaled insulin and extended zinc suspension insulin. On day 98 of inhaled insulin treatment, patient took extra inhaled insulin (3 mg extra at supper and 2 mg extra at bed). He also consumed two beers prior to bed. The next morning, he was found unresponsive, convulsing and sweating. Patient's girlfriend administered glucagon; ten minutes later BG was 386 mg/dL. In extension study 111, on day 508 of inhaled insulin treatment, patient went out in the evening with friends and had alcohol. After returning home, his serum glucose was 453 mg/dL at 2215, and he took 18 mg of inhaled insulin. At 0140 the next morning, he awoke and checked his blood sugar, which was 229 mg/dL. He gave himself 24 U of insulin glargine and 6 mg of inhaled insulin and went back to sleep. At 0700, he was found in bed convulsing; paramedics called. Serum glucose 20 mg/dL; D50 given. Transported to ER; released later that day. On day 558 of inhaled insulin administration, pt had

several drinks before bed. At 0540, patient awoke, sat in a chair, refused to return to bed, and then had a seizure and bit his tongue. Paramedics called; BG 38 mg/dL. IV dextrose given; patient did not regain consciousness and was transported to ER. In ER, he regained consciousness and was discharged later that day.

106-5030-6883: 53 yo woman with Type 1 DM, treated with inhaled insulin and extended zinc suspension insulin. On day 31 of inhaled insulin treatment, at 0900, patient was found unconscious by her roommate. Blood glucose was 20 mg/dL; paramedics administered IV dextrose at the scene. In the ER, patient's body temperature was 90 degrees Fahrenheit rectally. She was treated with additional dextrose, and was released to home that day.

106-5060-6966: 36 yo man with Type 1 DM, treated with inhaled insulin and extended zinc suspension insulin. On the morning of day 33 of treatment with inhaled insulin, after experiencing morning hypoglycemia for several days, the patient was found unresponsive by his wife. He was treated with glucagon and awoke within 15 minutes. Bedtime extended zinc insulin was moved from bedtime to morning. On the morning of day 39 of inhaled insulin, patient was found comatose with a blood sugar of 14 mg/dL. His wife administered 1 mg of glucagon. After three hours, patient's blood sugar "had stabilized". Patient permanently discontinued study in response to this event.

107-5007-7988: 19 yo woman with Type 1 DM, treated with inhaled insulin and isophane insulin. Had 12 reported severe hypoglycemic events. The first nine of these events were during a 3-week winter break from college. In these events, the patient's mother had difficulty waking the patient, and the patient responded to orange juice administered by the mother. In most cases, no blood sugar was measured prior to orange juice administration. The investigator felt that it was possible that patient had not been tightly controlling her blood sugars while away from home, with resultant hypoglycemic episodes when she resumed her intensive regimen while back at home. However, the three later events did have blood sugars measured at the time of the event; these values were 45, 49 and 43 mg/dL. All events were in the morning.

107-5052-7181: 53 yo man with Type 1 DM, treated with inhaled insulin and isophane insulin. On day 23 of inhaled insulin treatment, while driving home from work, patient became hypoglycemic and had a motor vehicle accident at around midnight, running into a ditch. He had not taken his evening isophane, but had taken his usual inhaled insulin dose at around 2000. The patient called his son, who drove the patient home. At 0600 the next morning, blood glucose was 67 mg/dL. The patient had also had three other episodes of hypoglycemia within the four weeks prior to the accident.

107-5083-7499: 17 yo boy with Type 1 DM, treated with inhaled insulin and isophane insulin. On day 8 of inhaled insulin administration, after playing basketball for 5 minutes, the patient became dizzy and vomited. Blood glucose measured 39 mg/dL. Pt consumed 2 glasses of orange juice, cake and milk. One hour later, BG 22 mg/dL. Patient's mother administered glucagon, and paramedics administered IV glucose. Pt hospitalized for hypoglycemia, vomiting and dehydration.

107-5127-7221: 30 yo woman with Type 1 DM, treated with inhaled insulin and isophane insulin. On the morning of day 19 of inhaled insulin treatment, patient had a grand mal seizure witnessed by her parents. Was given glucagon at the scene and recovered from the seizure. Blood sugar was not measured at the time of the event, but investigator felt seizure was due to hypoglycemia, and seizure responded to glucagon. On day 486 of inhaled insulin administration, at 2200, her roommate witnessed the patient become unconscious and then have a seizure. The roommate called an ambulance; patient's BG while still unconscious was 29 mg/dL. She regained consciousness after IV glucose, and she was not transported to the hospital. No change was made in her insulin regimen. On day 522 of inhaled insulin administration, the patient "passed out" and had a witnessed seizure at home. She was transported to the ER, where she was given IV glucose and discharged to home. No change was made in her inhaled insulin regimen. On day 527 of inhaled insulin administration, patient "fell unconscious" and had a seizure, that was witnessed by her roommate. The roommate called an ambulance; patient was treated with IV glucose, but was not transported to the hospital. No change in insulin regimen in response to event. On day 615 of inhaled insulin administration, patient was found at home by a friend; patient was unconscious and having a seizure. Treatment not mentioned. On day 632 of inhaled insulin administration, at 0400, patient had a blood sugar of <36 mg/dL and a seizure. An ambulance was called and the pt was treated with IV glucose. At 0600, her BG was 171 mg/dL. She was not admitted to the hospital and her insulin was not changed. On day 654, patient discontinued study. Although the reason for discontinuation was listed as "other", and not as "adverse event", the investigator's reason for discontinuation was "too many serious hypoglycemias (sic) caused by the study drug".

109-5071-0483: 66 yo man with Type 2 DM, treated with inhaled insulin monotherapy. On day 12 of inhaled insulin administration, at around 1800, took 6 mg inhaled insulin, but delayed eating. At appr 1900, wife noted patient to be perspiring profusely and unable to obey simple commands. Patient was taken to ER, where BG was 2.1 mmol/L (38 mg/dL). He was given IV dextrose and furosemide. He was released to home and inhaled insulin was resumed the next day.

111-5017-8450: 73 yo man with Type 2 DM, treated with inhaled insulin and isophane insulin. On day 469 of inhaled insulin administration, after taking his granddaughter to the park in the afternoon, he became disoriented and confused while driving home. He attempted to pull off to the side of the road, thought he applied his brakes, and had a motor vehicle accident. Paramedics measured a serum glucose of 52 mg/dL. He was given IV D50 with immediate response. In the ER, he was found to have a chest wall contusion, but no fractures. His inhaled insulin dose was reduced and he was discharged from the ER that night. He had also had a severe hypoglycemic event requiring emergency room treatment 3 days previously, and had a HbA1c of 5.9%.

111-5025-6592: see 106-5025-6592

111-5030-6883: 54 yo woman with Type 1 DM, treated with inhaled insulin and isophane insulin. On day 92 of inhaled insulin administration in Study 111, patient was found in her car on the side of the road at around 1800. She had sluggish speech and told paramedics that she was diabetic and had not eaten. She was given oral dextrose; BG after measured 20 mg/dL.

Taken to ER where she had altered level of consciousness. In the critical care unit, she was given 50 cc of dextrose; BG 39 mg/dL. Was discharged later that day. On day 111 of inhaled insulin in Study 111, had loss of consciousness and BG 29 mg/dL. Paramedics gave oral dextrose with reversal of symptoms. Four days later, was seen in the ER again with BG 20 mg/dL. Three days after that, was seen in ER again with BG 20 mg/dL and unresponsiveness; responded to D50.

111-5052-7180: 34 yo man with Type 1 DM, treated with inhaled insulin and isophane insulin. On day 103 of inhaled insulin administration in Study 111, patient began crying and speaking incoherently. Blood sugar was 30 mg/dL. Transported to hospital by paramedics; admitted. EEG and CT nl. ECG borderline ventriculomegaly. Discharged 2 days later.

111-5061-7793: 44 yo woman with Type 1 DM, treated with inhaled insulin and isophane insulin. On day 726 of inhaled insulin administration, patient did a large amount of house cleaning and ate soup for lunch. At 1430, she took a nap, and was found unconscious at 1800. An ambulance transported the patient to the hospital; blood sugar values at the time of the event are not mentioned. Patient received D50 in the ER and was discharged the same day. The narrative states that inhaled insulin treatment continued unchanged, but inhaled insulin was discontinued 10 days later.

111-5061-7794: 31 yo woman with Type 1 DM, treated with inhaled insulin and isophane insulin. In the early morning of day 303, patient had a severe hypoglycemic episode with unconsciousness and incontinence. She had not taken inhaled insulin at bedtime, but she had taken isophane insulin. She was transported to the ER, and received D50 in the ambulance. Blood sugar prior to transport was 38 mg/dL. The narrative does not mention hospital admission. On day 314 of inhaled insulin administration, patient awakened in the early morning, and was disoriented and not fully conscious. At 0445, her husband administered juice and licorice, but the patient remained disoriented. At 0449, the patient's blood sugar was 47 ng/dL. The husband gave the patient a glucagon injection, and the patient recovered by 0513. Inhaled insulin was not changed in response to these events.

111-5061-7797: 46 yo man with Type 1 DM, treated with inhaled insulin and isophane insulin. On day 479 of inhaled insulin administration, patient experienced gastroenteritis with nausea. He did not eat that day, and took his premeal inhaled insulin and hs inhaled and SQ isophane insulins. The next morning, at 0300, patient awoke feeling nauseated and weak. He got up to measure his blood sugar, fell down to the floor, and was unconscious for 5-10 seconds. His glucose measured 38 mg/dL. He drank two glasses of orange juice and felt better. At 0900, his blood sugar was 165 mg/dL. His inhaled insulin dose was not changed in response to the event.

111-5064-6103: 16 yo boy with Type 1 DM, treated with inhaled insulin and UL. On day 622 of inhaled insulin administration, patient developed nausea and vomiting shortly after midnight. His bedtime blood sugar had been 305 mg/dL. He was hospitalized with diabetic ketoacidosis, with a blood sugar of 705 mg/dL, beta-hydroxybutyrate of 12.8 mM/L, and large ketones in the urine. He was treated with IV fluids, potassium and regular insulin. Inhaled insulin was

discontinued. Two days later, he was discharged on lispro insulin and UL. He was discontinued from study due to this event.

111-5064-6519: see Serious Gastroenterologic Adverse Events

111-5064-6524: 16 yo boy with Type 1 DM, treated with inhaled insulin and UL. On day 294 of inhaled insulin administration, patient began vomiting at suppertime, and did not take his evening doses of either insulin. Admitted to the hospital with DKA on day 295 of inhaled insulin administration. Patient had large ketones in the urine, serum blood glucose >600 mg/dL, serum bicarbonate 8 mM/L, blood pH 7.19. Treated with fluids, potassium and regular insulin IV. Had renal insufficiency; creatinine value not reported. Withdrawn from study due to this event. narrative states patient had problems with noncompliance. Applicant's serious adverse event listing also states that patient had another serious episode of DKA on day 66 of inhaled insulin administration, but this event is not discussed in the narrative.

111-5066-7741: 41 yo woman with Type 1 DM, treated with inhaled insulin and isophane insulin. On day 323 of inhaled insulin administration, at 0230, while in bed, she was found by her husband to be incoherent, screaming, "cross-eyed" and clammy. The husband measured her blood sugar at 22 mg/dL, then injected glucagon without response. The glucagon was later found to have expired. An ambulance was called; the attendant administered oral glucose gel and then a glass of milk. At 0450, the patient's BG was 116 mg/dL. Her inhaled insulin was not changed.

111-5066-7745: 29 yo man with Type 1 diabetes, treated with inhaled insulin and extended zinc suspension insulin. On day 190 of inhaled insulin administration, at 0400, the patient awoke from sleep sweating, shaking and disoriented. Blood sugar was 35 mg/dL. Girlfriend gave patient orange juice, but he did not respond, and he began to have a seizure with tonic-clonic movements. An ambulance was called, and the attendants gave the patient IV dextrose; he was coherent within 15 minutes and remained at home. Inhaled insulin was not changed.

111-5070-6896: 30 yo woman with Type 1 DM, treated with inhaled insulin and isophane insulin. On the morning of day 137 of inhaled insulin administration, the patient's mother found the pt unresponsive. The mother put jam on the patient's tongue, and the patient aroused somewhat, but did not become coherent. The patient was transported to the ER by ambulance; she received 50% dextrose in the ER. By 1135, the patient's BG was 255 mg/dL, and she was discharged to home following lunch. Both her inhaled insulin and isophane insulin were reduced in response to this event.

111-5070-6898: 42 yo woman with Type 1 DM, treated with inhaled insulin and extended zinc suspension insulin. On day 304 of inhaled insulin administration, patient experienced a hypoglycemic event from 0030-0800 hours. Her husband reported that she was convulsing, combative and stuporous. Blood sugars were not measured during the event. Her husband did not bring her to the hospital, but gave her a glass of juice and watched her through the night. Patient's prebreakfast glucose that morning was 38 mg/dL. The patient went to work the next day, but had a headache, was sweaty and felt tired. Both her inhaled insulin and isophane insulin

doses were decreased in response to this event. The status of her marriage after the event was not mentioned.

111-5081-6446: 18 yo woman with Type 1 DM, treated with inhaled insulin and extended zinc suspension insulin. On day 230 of inhaled insulin administration, at 0100, the patient's blood glucose was 74 mg/dL; she took her extended zinc insulin, but did not take her bedtime inhaled insulin. She went to bed at 0200. At 1600, she had not awakened, and her roommates became concerned and tried to wake her. She awoke but was incoherent. Her roommates tried to test her blood sugar, but dropped and broke her meter. Paramedics transported the patient to the ER, where she was treated the patient with 50% dextrose. After dextrose, blood sugar was 130 mg/dL. She was discharged to home from the ER.

111-5082-3341: 11 yo girl with Type 1 DM, treated with inhaled insulin and insulin glargine. On day 831 of inhaled insulin administration, the patient did not eat supper. At 2144, her BG was 375 mg/dL, and she received 40 units of insulin glargine. The next morning at 0028, her blood sugar was 58 mg/dL; intervention not mentioned. At 0830, she was unarousable. Her mother gave her glucagon and called paramedics. At 0847, after glucagon, BG was 117 mg/dL. At 0900, she had a seizure and was transported to the hospital. She was treated with IV fluids, observed overnight, and discharged the next day. Inhaled insulin was not changed; glargine dose reduced.

111-5082-3346: 10 yo boy with Type 1 DM, treated with inhaled insulin and insulin glargine. On day 657 of inhaled insulin administration, patient had gastroenteritis with diarrhea and vomiting. His blood sugars fluctuated through the day; inhaled insulin was continued. Prior to bedtime, he experienced a hypoglycemic episode and was taken by ambulance to the hospital, where his BG was 27 mg/dL. He was admitted and treated with IV glucose. His inhaled insulin and insulin glargine doses were reduced in response to this event. He was discharged to home two days after admission.

111-5082-3347: 8 yo boy with Type 1 DM, treated with inhaled insulin and extended zinc suspension insulin. On day 346 of inhaled insulin administration, the patient had a large late breakfast at 0920, with his usual pre-breakfast dose of 6 mg inhaled insulin. At 1300 (no lunch yet), the patient's mother observed the patient having a seizure. BG measured at 60 mg/dL. Mother administered glucagon and took patient to hospital, where he was admitted. He was treated with intravenous fluids and intravenous insulin. He was discharged the next day and his inhaled insulin was resumed.

111-5082-3348: 9 yo boy with Type 1 DM, treated with inhaled insulin and insulin glargine. On day 310 of inhaled insulin administration, after attending a football daycamp that ended at 1600, he called his mother when he arrived home and told her that he did not feel well. His mother arrived home at 1800 and found the patient standing in the shower, confused, flailing his arms, and unable to stand on his left leg. BG was 39 mg/dL. He was taken to the ER, where his BG was 59 mg/dL. He was admitted to the hospital and treated with IV dextrose 5% (sic) and normal saline. A head CT at 1920 revealed a left middle cranial fossa arachnoid cyst, but was otherwise "negative". He was discharged to home the next day. On inhaled insulin day 445, the

patient exercised strenuously for several hours, and had three meals and three snacks. At bedtime, his blood sugar was 82 mg/dL; he ate an ice cream sundae and took 7 units of insulin glargine. At 0100 the next morning, he was found "foaming at the mouth", limp, and unresponsive. His pupils were dilated and he had severe sweating. BG was 46 mg/dL; mother administered glucagon and glucose increased to 140 mg/dL. Paramedics administered orange juice and glucose gel and transported the patient to the ER. Upon arrival, his BG was 119 mg/dL, but dropped to 38 mg/dL at 0213. He was treated with intravenous glucose, and released at 0500. Inhaled insulin was not changed, but glargine was reduced. Head CT in ER revealed unchanged left middle cranial fossa arachnoid cyst. On day 578 of inhaled insulin treatment, while at a sleepover at a friend's house, his friend's mother heard noises from the bedroom and called 911. The principle investigator believed these noises to be seizure activity. Paramedics gave the patient glucagon and transported him to the hospital. BG was 40 mg/dL. He was admitted and treated with IV fluids and dextrose. He was discharged one day after this event.

111-5087-7011: 17 yo boy with Type 1 DM, treated with inhaled insulin and isophane insulin. On day 1156 of inhaled insulin administration, he awoke with BG 45 mg/dL. He drank juice, then administered isophane and inhaled insulins, then ate breakfast. At school, he attended a vigorous gym class. At 0900, he was confused and disoriented. He was given two juices and transported to the ER. He was treated and released later that day. He did not recall the event. Neither insulin was changed in response to this event.

111-5088-3384: 7 yo girl with type 1 DM, treated with inhaled insulin and isophane insulin. On day 190 of inhaled insulin administration, BG at 2115 was 456 mg/dL. By study regimen, pt should have received snack followed by 1 mg inhaled and 5 units isophane insulins, and study site should have been called for BG >400 mg/dL. Blood sugar should have been checked 2.5-3 hours postdose. However, pt was not given snack and was given 3 mg inhaled and 5 u isophane. Site was not called. In the early morning of the next day, patient experienced a seizure and her sister awakened the patient's parents. BG was 47 mg/dL at 0243. Parents gave patient juice and called paramedics. BG at 0253 was 57 mg/dL; by 0304, BG was 205 mg/dL. Patient was not transported to the hospital.

111-5089-3025: 10 yo girl with Type 1 DM, treated with inhaled insulin and NPH. On day 41 of inhaled insulin administration, patient stopped keeping BG and dosing logs. On day 53, patient stopped taking her lunchtime insulin while at school. On day 67, she began to vomit and was hospitalized for DKA. She was treated with intravenous insulin, and DKA resolved 3 days later. Inhaled insulin was permanently discontinued on hospital admission.

111-5091-3008: 11 yo boy with Type 1 DM, treated with inhaled insulin and extended zinc suspension insulin. On day 140 of inhaled insulin administration, patient received 4 mg of inhaled insulin and 14 units of extended zinc suspension insulin at 2200. At midnight, pt experienced a seizure. Mother administered glucagon and patient "stabilized". In ER at 0230, BG was 46 mg/dL; IV fluids started. By 0500, BG was 138 mg/dL. Pt had morning inhaled insulin and ate breakfast, then was released to home. No action was taken with regard to inhaled insulin.

111-5094-7094: 14 yo boy with Type 1 DM, treated with inhaled insulin and extended zinc suspension insulin. On day 598 of inhaled insulin administration, at 2000, patients BG was 65 mg/dL. At 2200, he ate two chocolate chip pancakes and took 3 mg of inhaled insulin. The next morning, at 0700, he was pale, combative and incoherent with a BG of 33 mg/dL. Paramedics treated patient with IV saline and 25 gms D50. 30 minutes after treatment, BG was 255 mg/dL, and "the event was considered resolved".

111-5095-3334: 7 yo boy with Type 1 DM, treated with inhaled insulin and extended zinc suspension insulin. On day 596 of inhaled insulin administration, family was advised to increase insulin dose (type of insulin not specified) for a BG of 300 mg/dL. On days 598 and 599, pt had low blood sugar readings; family was advised to decrease insulin back to prior regimen. At 2100 on day 599, patient was brought to the ER for hypoglycemia (BG not mentioned). He was admitted, treated with intravenous fluids, and released the next day. Inhaled insulin was temporarily discontinued, but later resumed. Zinc suspension insulin dose reduced.

111-5096-3358: 12 yo boy with Type 1 DM, treated with inhaled insulin and extended zinc suspension insulin. On day 584 of inhaled insulin administration, at 1800, the patient had a blood sugar of 55 mg/dL and was given a snack and 3 mg of inhaled insulin. At 2247, BG was 81; pt given juice. The next morning at 0900, pt appeared confused. BG was 59 mg/dL and pt was given juice. He sat on the floor and began to cry. He stopped crying, and his legs then began to twitch. At 0934, his BG was 78 mg/dL. The mother called the study site; the investigator felt the patient might have been having a partial seizure. At 1015, pt taken to ER; BG 109 mg/dL, but speech slurred. At 1120, pt vomited and had a bowel movement. Pt was given an antibiotic "as a precaution". By 1330, pt was able to recognize people and verbalize coherently. He was admitted to the hospital. A neurologist ruled out meningitis, and felt the event had been a partial seizure due to hypoglycemia. Patient was discharged to home the next day.

111-5096-3359: 10 yo boy with Type 1 DM, treated with inhaled insulin and extended zinc suspension insulin. On day 435 of inhaled insulin administration, at 0500, the patient had a seizure m/b profuse perspiration, gurgling, "eyes that rolled back", and a rigid upper body. Did not respond to glucagon injection and glucose gel. Paramedics called; measured glucose at 46 mg/dL. Upon arrival at ER, BG 204 mg/dL. Treated with IV fluids and glucagon. Had 2 episodes of vomiting and one episode of diarrhea. Admitted to hospital; "event was considered resolved the same day". Inhaled insulin dose was not changed in response to this event.

111-5098-3048: 9 yo boy with Type 1 DM, treated with inhaled insulin and glargine insulin. On day 380 of inhaled insulin administration, at 0600, he was found having a seizure in the shower. Manifestations included whole body jerking, blue lips, and inability to speak. The patient was taken to the ER, where his blood glucose was 85 mg/dL at 0620. MRI and EEG normal. He was discharged later that day. On day 669 of inhaled insulin administration, at 0611, patient's blood glucose was 52 mg/dL at 0611; at 0615, he had a seizure. Two hours after the seizure, he saw the study investigator, who reduced his insulin glargine, but did not change his inhaled insulin.

111-5127-7224: 60 yo man with Type 1 DM, treated with inhaled insulin and isophane insulin. On day 667 of inhaled insulin treatment, patient started a new job and did not eat an afternoon snack. Patient's wife was unable to awaken patient from a nap at 1800; wife called ambulance. Patient was unconscious for approximately 30 minutes; was given D50 by paramedics with "good response". No change in inhaled insulin in response to event.

Serious Neoplastic Adverse Events

1001-0005-1029: 49 yo man with Type 2 DM, treated with inhaled insulin and glibenclamide. On inhaled insulin Day 351, to ear, nose and throat physician (ENT) for hoarseness; vocal cord polyp noted. Polyp removed; hoarseness persists. Inhaled insulin not interrupted.

A2171002-0119-5236: 67 yo man with Type 2 DM, treated with inhaled insulin, metformin and pioglitazone. On day 663 of inhaled insulin, right upper lobe "shadowing" noted on chest X-ray (CXR). Found to have poorly differentiated (possibly squamous) bronchial carcinoma metastatic to thoracic wall. Chemotherapy initiated. Applicant states patient had history of occupational asbestos exposure. Applicant states patient quit smoking 25 years prior to event, but prior to that had smoked up to 60 cigarettes per day. Inhaled insulin discontinued on study day 677; oral agents continued. Also had declines in FEV1 and DLco.

A2171002-0141-8060: 68 yo woman with Type 2 DM, treated with inhaled insulin and metformin. On inhaled insulin day 638, chronic myelogenous leukemia diagnosed. On Study Day 726, experienced blast crisis and was discontinued from study. Was also a seroconverter for anti-insulin antibodies, and had a decline in DLco.

A2171022-5098-3258: 47 yo female with Type 1 DM, treated with inhaled insulin and isophane. On day 105 of inhaled insulin administration, a breast biopsy was performed, and on day 141, breast surgery was performed with a diagnosis of lobular breast carcinoma *in situ*. Inhaled insulin was discontinued on Study Day 188 due to the cancer.

A2171029-1085-3554: 73 yo man with Type 2 DM, treated with inhaled insulin and isophane. On day 59 of inhaled insulin treatment, prostate cancer diagnosed; screening physical exam had been normal. Discontinued study on Day 69 due to cancer.

111-5041-8024: 62 yo man with Type 2 DM, treated with inhaled insulin. On day 256 of inhaled insulin, began to experience anorexia, weakness and back pain. Presented to ER on day 267; CT revealed two lung nodules and a large mass and cyst on right kidney. Colon cancer diagnosed on colonoscopy; metastases to lung. Also diagnosed with renal cancer, and underwent surgery. Colon cancer inoperable. Pt received chemotherapy. Inhaled insulin discontinued due to cancer.

111-5042-8002: 74 yo man with Type 2 DM, treated with inhaled insulin and Ultralente®. On day 510 of inhaled insulin treatment, pt was hospitalized with severe back pain. MRI revealed tumor lower spine. At surgery, found extranodal lymphoma with pathological fracture at L3. Treated with chemotherapy; inhaled insulin discontinued due to cancer on day 588.

111-5060-0672: 73 yo man with Type 2 DM, treated with inhaled insulin monotherapy. On Day 658 of inhaled insulin treatment, patient experienced retrosternal chest pain and was hospitalized for a myocardial infarction. During that evaluation, he was noted to have a rectal mass, which was biopsied and found to be a "malignant rectal tumor". Inhaled insulin was temporarily discontinued during the patient's hospitalization, then resumed for 5 days, then permanently discontinued. Patient underwent excision of the rectal tumor 29 days after discontinuation of inhaled insulin, and suffered another myocardial infarction on the same day as the surgery. Further treatment for and outcome of the rectal tumor are not included in the narrative.

111-5127-0656: 72 yo man with Type 2 DM, treated with inhaled insulin, glibenclamide and metformin. On day 546 of inhaled insulin administration, patient developed deep coughing and hemoptysis. On day 558, a right apical lung mass was noted on CXR. In retrospect, a right apical mass may have been present on a CXR done on day 432. Chest CT on day 574 revealed 6.0x6.9 cm solid soft tissue mass in right apex with evidence of rib destruction. Biopsy on day 587 revealed squamous cell lung carcinoma. Inhaled insulin was permanently discontinued in response to this event. At time of reporting, lung cancer was still ongoing. Patient had history of smoking (25-30 years of up to two packs per day).

Serious Neurologic Adverse Events

103-5041-0022: 64 yo man with Type 2 DM, treated with inhaled insulin and Ultralente®. On day 88 of inhaled insulin, experienced a CVA with complete aphasia; bradycardia and premature ventricular contractions (PVCs) also noted. Pt was permanently discontinued from study. 18 days after CVA, pacemaker placed for bradycardia. 40 days after CVA, CT revealed left cerebral hematoma. Persistent word-finding problems and use of walker.

103E-5002-0089: 62 yo man with Type 2 DM, treated with inhaled insulin and extended zinc suspension insulin. On day 1,741 of inhaled insulin treatment, patient was admitted to hospital with a CVA. Manifestations of CVA not described. He was discontinued from study drug; CVA considered resolved 19 days after CVA presentation.

104E-5016-0006: 61 yo woman with Type 2 DM, treated with inhaled insulin, metformin and glibenclamide. On day 1302 of inhaled insulin treatment, patient developed severe paraplegia attributed to spinal cord ischemia. No further details in narrative. Permanently discontinued inhaled insulin 6 days later.

111-5029-0437: 58 yo man with Type 2 DM, treated with inhaled insulin, glipizide and metformin. On day 618 of inhaled insulin administration, pt presented to ER with disorientation and dizziness. ECG negative; discharged to home. Returned 2 days later; MRI showed left cerebellar infarct. Discharged two days later with no residual neurologic deficit. Permanently discontinued inhaled insulin at the time of this event.

111-5072-0507: 72 yo man with Type 2 DM, treated with inhaled insulin and metformin. On day 478 of inhaled insulin administration, patient complained of a sore neck and feeling unwell.

He then vomited. He was transported to the ER by ambulance, where a CT revealed subarachnoid hemorrhage within the right sylvian fissure. He was transferred to the intensive care unit and then underwent a left frontotemporal craniotomy with clipping of a left middle cerebral artery aneurysm. Inhaled insulin was permanently discontinued on admission. Six days later, he experienced cerebral vasospasm; the narrative does not mention symptoms. On that day, he also was diagnosed with aspiration pneumonia. During this hospitalization, he also experienced a subdural hematoma and a pulmonary embolism. He was transferred to a rehabilitation center 75 days after the subarachnoid bleed, and was discharged to home 22 days later. His final neurologic status was not mentioned in the narrative.

Serious Reproductive and Urologic Events

A2171007-5141-0006: 29 yo woman with Type 2 pregestational DM, treated with inhaled insulin, enrolled in PK/PD study in pregnant patients with gestational or pregestational DM. Enrolled at 36 weeks EGA. On Study Day 1, received a single 3 mg dose of inhaled insulin. On Study Day 6, was admitted to the hospital for her second planned study admission. She did not receive another dose of inhaled insulin. About 1.5 hours after admission, had rupture of amniotic membranes. Fetal heart rate was reported as "good", but speculum examination revealed prolapsed umbilical cord. Underwent emergent C-section that night and was delivered of a 4 lb 11 oz male infant, APGAR (activity, pulse, grimace, appearance, respiration) scores 6 at 1 minute and 8 at 5 minutes. The mother was withdrawn from the study. On post-treatment day 29, the patient presented with a 24 hour history of headache, and MRI revealed a sagittal sinus thrombus. Admitted and received intracranial thrombolytic therapy and peripheral anticoagulation. Recovered and was discharged one week later.

REFERENCES

Basu A et al 2005. Insulin autoimmunity and hypoglycemia in seven white patients. Endocr Pract 11(2):97-103

Beisswenger P et al 2004. Prandial glucose regulation in the glucose triad: emerging evidence and insights. Endocrine 25(3):195-202

Bindra S and Cefalu W 2002. Exubera®. Inhale Therapeutic Systems. Curr Opin Investig Drugs 3 (5):758-62

Diabetes Control and Complications Trial Research Group 1993. The effect of intensive treatment of diabetes on the development and progression of longterm complications in insulin-dependent diabetes mellitus. NEJM 329:977-86

Dunger D et al 2004. ESPE/LWPES consensus statement on diabetic ketoacidosis in children and adolescents. Arch Dis Child 89:188-94

Edge J et al 2001. The risk and outcome of cerebral oedema developing during diabetic ketoacidosis. Arch Dis Child 85:16-22

Edge J et al 1999. Causes of death in children with insulin dependent diabetes, 1990-1996. Arch Dis Child 81:318-23

Egger M et al 1997. Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a metaanalysis. Diabet Med 14 (11):919-28

Harrison's Textbook of Internal Medicine, 16th Ed, accessed via StatRef 27 Jun 05.

Heinemann L 2002. Variability of insulin absorption and insulin action. Diabetes Technology and Therapeutics 4(5):673-82

Jeffcoate S 2004. Diabetes control and complications: the role of glycated haemoglobin, 25 years on. Diabet Med 21(7):657-65

Levitsky L et al. Death from diabetes in hospitalized children (1970-1988). Pediatr Res 29:A195

Miodovnik M et al 1988. Periconceptual metabolic status and risk for spontaneous abortion in insulin-dependent diabetic pregnancies. Am J Perinatol 5(4):368-73

Moxness M et al 2002. Development and validation of radioligand binding assays to measure total IgA, IgE, IgG and IgM insulin antibodies in human serum. Diab Metab Research Reviews 18(S4):S21

Muller W 1998. Diabetes mellitus- longterm survival. J Insurance Med 30:17-27

Rosenn B et al 1994. Glycemic thresholds for spontaneous abortion and congenital malformations in insulin-dependent diabetes mellitus. Obstet Gynecol 84(4):515-20

Royle P et al 2004. Inhaled insulin in diabetes mellitus. Cochrane Database Syst Rev 2004(3):CD003890

van Haeften T et al 1987. Adverse effects of insulin antibodies on postprandial plasma glucose and insulin profiles in diabetic patients without immune insulin resistance. Diabetes 36:305-9

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